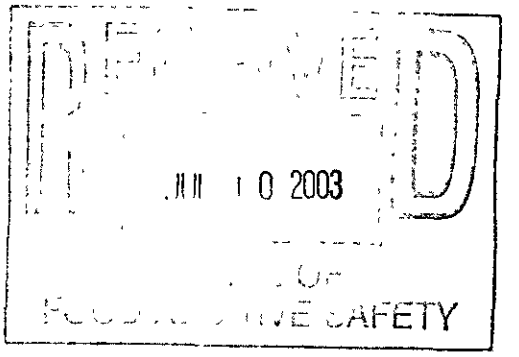
GR

ORIGINAL SUBMISSION



FEDERAL EXPRESS

July 10, 2003

Dr Allan Rulis, Ph.D.
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food And Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

AAC CONSULTING GROUP

7361 Calhoun Place,
Suite 500
Rockville, Maryland 20855-2765
301 838 3120
fax 301 838 3182

Re: GRAS Notice: ε-Polylysine For Addition To Specified Foods

Dear Dr Rulis.

In accordance with proposed 21 CFR 170 36 (Notice of a claim for exemption based on a GRAS determination) published in the Federal Register (62 FR 18939-18964), I am submitting in triplicate, as the agent to the notifier, Chisso Corporation, Forefront Tower II, 13-1 Kachidoki 3-chome, chuo-ku, Tokyo, Japan, 104-8555, a GRAS notification of ε-polylysine for use as an antimicrobial food preservative ingredient, a GRAS panel report setting forth the basis for the GRAS determination, and CV's of the members of the GRAS panel (Dr. W. Garry Flamm, Dr. Douglas Archer, and Dr. Donald Hughes) for review by the agency.

Data supporting the safety of ε-polylysine as a preservative was published in Regulatory Toxicology and Pharmacology 37 (2003) 328-340.

Sincerely

Edward A Steele
Vice President
Food, Dietary Supplement & Cosmetic Consulting

Enclosures

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AAC
CONSULTING GROUP

ε-POLYLYSINE NOTIFICATION

I. GRAS Exemption Claim

A. Claim of Exemption From The Requirement for Premarket Approval Requirements Pursuant to Proposed CFR § 170.36(c)(1)

ε-Poloylysine has been determined to be generally recognized as safe, and therefore, exempt from the requirement of premarket approval, under the conditions of its intended use as described below. The basis for this finding is described in the following sections.

Signed,

Date 7/10/03

Edward A. Steele

Agent for:

Chisso Corporation
Forefront Tower II
13-1 Kachidoki 3-chome, chuo-ku
Tokyo, Japan, 104-8555

ε-POLYLYSINE NOTIFICATION

B. Name and Address of Notifier

Edward A Steele
Vice President, Food, Dietary Supplement & Cosmetic Consulting
AAC Consulting Group
7361 Calhoun Place, Suite 500
Rockville, MD 20855-2765
Telephone. 301-838-3182
Facsimile: 301-838-3182

C. Common or Usual Name of the Notified Substance

ε-Polylysine

D. Conditions of Use

The intended use of the ε-polylysine is to serve as an antimicrobial agent or preservative as defined in 21 CFR §170 3 (o)(2) This section refers to substances used to preserve food by preventing growth of microorganisms and subsequent spoilage The foods that are proposed for ε-polylysine addition are cooked rice and sushi rice The proposed levels of addition are from 5 to 50 ppm ε-polylysine

E. Basis for the GRAS Determination

Pursuant to 21 CFR § 170 30 ε-polylysine has been determined to be GRAS by scientific procedures. This determination is based on the views of experts who are qualified by scientific training and experience to evaluate the safety of ingredients used in food. (See Attached Expert Panel Statement – DETERMINATION OF THE GRAS STATUS OF ε-POLYLYSINE FOR ADDITION TO SPECIFIED FOODS)

F. Availability of Information

The data and information that serve as a basis for this GRAS are available for the Food and Drug Adminsitration's review and copying during reasonable business hours at the offices of:

Edward A. Steele
AAC Consulting Group
7361 Calhoun Place, Suite 500
Rockville, MD 20855-2765
Telephone· 301-838-3182
Facsimile 301-838-3182

ε-POLYLYSINE NOTIFICATION

II. Detailed Information About the Identity of the Substance

A. Identity

ε-Polylysine is a homopolymer of L-lysine, one of the essential amino acids. The chemical formula for ε-polylysine is shown in Figure 1. The systematic name of ε-polylysine is poly(imino(2-amino-1-oxo-1,6-hexanediyl)).

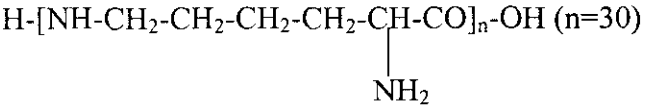

Figure 1. Chemical formula of ε-polylysine

The emperical formula for the typical ε-polylysine homopolymer is $C_{180}H_{362}N_{60}O_{31}$ with a molecular weight of approximately 4700 The Chemical Abstracts Service (CAS) Number for ε-polylysine is 28211-04-3.

B. Method of Manufacture

ε-Polylysine is prepared from a fermentation process using *Streptomyces albulus* under aerobic conditions The biotechnological process for producing ε-polylysine has been described in a U.S Patent Number 5,900,363 The fermentation is conducted according to recognized principles of current Good Manufacturing Practice. The raw materials used in bacterial cultivation and ε-polylysine synthesis are commonly used in bacterial fermentation production such as glucose, ammonium sulfate and yeast-malt extract.

Following fermentation, the culture media is filtered by a membrane filter to remove any microorganisms This filrate is further purified by passing it through an ion exchange resin, followed by treatment with activated charcoal (trade name: Shirasaegi FA-50W, Takeda Pharmaceutical Co.). Three ionic-exchange resins are used sequentially in the purification process. a weak acid, carboxyl cationic- exchange resin (Amberlite IRC-50, Rohm & Hass, eluent was 0.2M NaOH); a strong base, $-N(CH_3)_3$ anionic-exchange resin (Amberlite IRA-402, Rohm & Hass, eluent was water), and a strong acid (-SO3) cationic-exchange resin (Amberlite XT 1006, Rohm and Hass, eluent was water). The product is concentrated from the liquid media by evaporation The resulting ε-polylysine solids are powdered or atomized to provide the desired fine powder product form.

C. Specifications for ε-polylysine

Assay	98% purity
Description	Hygroscopic yellow powder
Solubility	Soluble in water and alcohol
Identification	CAS No. 28211-04-3
Heavy metals	Max 20 ppm
Arsenic	Max. 4 ppm
Lead	Max. 5 ppm
Residue on ignition	Less than 1%
Loss on drying	Less than 10%

III. Self-Limiting Levels of Use

According to USDA (1991), the 90th percentile consumption of rice in the U.S. is 300 g/day. If ε-polylysine was added at the maximum level of 50 ppm, then an individual consuming 300 g of rice would have an ε-polylysine intake of 15 mg or 0.25 mg/kg/day for a nominal 60 kg person. As the pharmacokinetic data demonstrate, approximately 75% of administered ε-polylysine radiolabel associated with each carbon in the lysine chain was excreted in the feces and not absorbed (Tokai Research, 1995a). Metabolism studies have further shown that less than 1% of the radiolabel recovered in the plasma sample was in the form of polylysine or polymeric fragments such as the 4 or 6 mer. Further metabolism studies suggest that L-lysine is cleaved from the homopolymer in the gastrointestinal tract and the freed lysine amino acid is further degraded in the lower gut or liver to α-aminoadipate and α-ketoadipate metabolites. Therefore, the data indicate there is very little systemic exposure to ε-polylysine.

The potential intake of L-lysine from ε-polylysine is minimal compared to intake of this amino acid from protein In a typical protein meal containing 50 g of meat, approximately 6% of total protein or 3 g of L-lysine would be ingested. This is 200 fold more than the likely maximum daily intake of L-lysine from ε-polylysine if all the homopolymer was digested into L-lysine, which clearly does not occur

4. Detailed Summary of the Basis for the Notifier's Determination that ε-polylysine is GRAS

An independent panel of recognized experts, qualified by their scientific training and relevant national and international experience to evaluate the safety of food and food ingredients, was

requested by Chisso Corporation to determine the Generally Recognized As Safe (GRAS) status of ε-polylysine for use as a antimicrobial food preservative ingredient. A comprehensive search of the scientific literature for safety and toxicity information on ε-polylysine was conducted through April 2003 and made available to the Expert Panel The Expert Panel independently evaluated materials submitted by Chisso Corporation and other materials deemed appropriate or necessary. Following independent, critical evaluation, the Expert Panel conferred and unanimously agreed to the decision described in the attached Expert Panel Statement – DETERMINATION OF THE GRAS STATUS OF ε-POLYLYSINE FOR ADDITION TO SPECIFIED FOODS).

EXPERT PANEL STATEMENT

DETERMINATION OF THE *GRAS* STATUS OF ε-POLYLYSINE FOR ADDITION TO SPECIFIED FOODS

The undersigned, an independent panel of recognized experts (hereinafter referred to as Expert Panel), qualified by their scientific training and relevant national and international experience to evaluate the safety of food and food ingredients, was requested by Chisso Corporation to determine the Generally Recognized As Safe (GRAS) status of ε-polylysine for use as a antimicrobial food preservative ingredient A comprehensive search of the scientific literature for safety and toxicity information on ε-polylysine was conducted through May 2003 and made available to the Expert Panel. The Expert Panel independently evaluated materials submitted by Chisso Corporation and other materials deemed appropriate or necessary Following independent, critical evaluation, the Expert Panel conferred and unanimously agreed to the decision described herein

Introduction

ε-Polylysine is approved for food use in Japan as an antimicrobial preservative (Ministry of Health, Labour and Welfare List of Existing Food Additives) and has been used for years For sliced fish and fish sushi, it is sprayed or dipped on the fish at levels of 0 1-0 5% (up to 5000 ppm) It is used in many traditional Japanese daily dishes (Nimono) at levels of 0 05% (500 ppm) Other commonly eaten Japanese foods that ε-polylysine is added at levels of 0 02-0 05% (200-500 ppm) include boiled rice, noodle soup stocks, other soups, noodles and cooked vegetables It is also used in sukiyaki (Japanese beef steak), potato salad, steamed cakes and custard cream. As these examples show, ε-polylysine has a history of use as an antimicrobial in multiple foods in Japan, including several staples of the Oriental diet

Identification and Composition

ε-Polylysine is a homopolymer of L-lysine, one of the essential amino acids The chemical formula for ε-polylysine is shown in Figure 1 The systematic name of ε-polylysine is poly(imino(2-amino-1-oxo-1,6-hexanediyl))

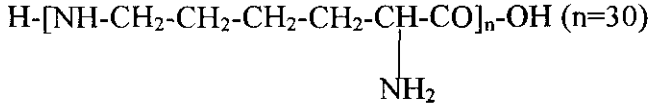

Figure 1. Chemical formula of ε-polylysine

ε-Polylysine has a molecular formula for the typical homopolymer molecule of $C_{180}H_{362}N_{60}O_{31}$ and a molecular weight of approximately 4700

More than 20 years ago the Gram-positive bacterium *Streptomyces albulus* ssp *lysinopolymerus* strain 346 was isolated from Japanese soil This strain was able to excrete polylysine into the medium at concentrations of up to 4–5 g/l (Shima and Sakai 1977) Later a mutant of strain 346 was isolated which produced four times higher amounts of ε-polylysine (Hiraki *et al* 1998) *Streptomyces albulus* is classified as a non-pathogenic microorganism of the Order Actinomycetales and Family Streptomycetaceae First isolated in 1982 from soil, its sole commercial use is for ε-polylysine production as it is the only organism that has been found to produce ε-polylysine

ε-Polylysine is produced by aerobic bacterial fermentation by *Streptomyces albulus*. FDA has approved the use of fermentation by-products of other non-pathogenic and non-toxicogenic *Streptomyces* species such as *S griseus* (21 CFR 184 1945) for cyanocobalamin production and *S rubinoginosis, S. olivaceus* and *S olivochromogenes* (21 CFR 184 1372) for insoluble glucose isomerase enzyme production

Specifications of ε-Polylysine

Specifications for ε-polylysine are given below in Table 1

TABLE 1
Specifications for ε-polylysine

Assay	98% purity
Description	Hygroscopic yellow powder
Solubility	Soluble in water and alcohol
Identification	CAS No 28211-04-3
Heavy metals	Max 20 ppm
Arsenic	Max 4 ppm
Lead	Max 5 ppm
Residue on ignition	Less than 1%
Loss on drying	Less than 10%

Manufacturing Process

ε-Polylysine is prepared from a fermentation process using *Streptomyces albulus* under aerobic conditions The biotechnological process for producing ε-polylysine has been described in a U S Patent Number 5,900,363 The fermentation is conducted according to recognized principles of current Good Manufacturing Practice The raw materials used in bacterial cultivation and ε-polylysine syntheses are commonly used in bacterial fermentation production such as glucose, ammonium sulfate and yeast-malt extract

Following fermentation, the culture media is filtered by a membrane filter to remove any microorganisms This filrate is further purified by passing it through an ion exchange resin, followed by treatment with activated charcoal (trade name Shirasaegi FA-50W, Takeda Pharmaceutical Co) Three ionic-exchange resins are used sequentially in the purification process a weak acid, carboxyl cationic- exchange resin (Amberlite

IRC-50, Rohm & Hass, eluent was 0 2M NaOH), a strong base, -$N(CH_3)_3$ anionic-exchange resin (Amberlite IRA-402, Rohm & Hass, eluent was water), and a strong acid (-SO3) cationic-exchange resin (Amberlite XT 1006, Rohm and Hass, eluent was water) The product is concentrated from the liquid media by evaporation The resulting ε-polylysine solids are powdered or atomized to provide the desired fine powder product form

Use and exposure to ε-polylysine

The intended use of the ε-polylysine is to serve as an antimicrobial agent or preservative as defined in 21 CFR 170 3 (o)(2) This section refers to substances used to preserve food by preventing growth of microorganisms and subsequent spoilage The foods that are proposed for ε-polylysine addition are cooked rice and sushi rice. The proposed levels of addition are from 5 to 50 ppm ε-polylysine

According to USDA (1991), the 90th percentile consumption of rice in the U S is 300 g/day If ε-polylysine was added at the maximum level of 50 ppm, then an individual consuming 300 g of rice would have an ε-polylysine intake of 15 mg or 0 25 mg/kg/day for a nominal 60 kg person As the pharmacokinetic data below demonstrate (Table 2), approximately 94% of administered ε-polylysine radiolabel associated with each carbon in the lysine chain was excreted in the feces and not absorbed (ADME/TOX, 2001) Metabolism studies have further shown that less than 1% of the radiolabel recovered in the plasma sample was in the form of polylysine or polymeric fragments such as the 4 or 6 mer Further metabolism studies suggest that L-lysine is cleaved from the homopolymer in the gastrointestinal tract and the freed lysine amino acid is further degraded in the lower gut or liver to α-aminoadipate and α-ketoadipate metabolites Therefore, the data indicate there is very little systemic exposure to ε-polylysine from oral ingestion

The potential intake of L-lysine from ε-polylysine is minimal compared to intake of this amino acid from protein In a typical protein meal containing 50 g of meat, approximately 6% of total protein or 3 g of L-lysine would be ingested This is 200 fold more than the likely maximum daily intake of L-lysine from ε-polylysine if all the homopolymer was digested into L-lysine, which clearly does not occur

Safety Studies

A publication by Hiraki et al (2003) (Attachment 1) provides a detailed description of the methods and results of the acute toxicity, bacterial mutagenicity and all absorption, distribution, metabolism and excretion studies described in this section The article also presents HPLC profiles of ^{14}C labeled polylysine and metabolites in plasma, feces and urine and ^{14}Clysine in plasma In addition, the subchronic and chronic toxicity studies were summarized and an assessment of safety for the proposed use was presented in this peer-reviewed journal

Absorption, distribution and metabolism

The pharmacokinetics and metabolism of ε-polylysine have been extensively characterized in four studies in rats The absorption, distribution and excretion of ^{14}C radiolabelled ε-polylysine was investigated in a pilot study with one Sprague-Dawley male rat administered 100 mg/kg *via* gavage (Tokai Research, 1995a) The ^{14}C radiolabel was present on all carbons in the lysine chain The rat was held in a glass metabolic cage for collection of urine, feces and expired air at hours 0-4, 4-8, 8-24 and every 24 hours afterwards for seven days post-dosing Blood was collected at 30 minutes, 1,2, 4, 6, 8 and 24 hours and every 24 hours thereafter for seven days Additional male rats were sacrificed at 8, 24 and 168 hours for whole body autoradiography After the administration of ε-polylysine, peak accumulation of radioactivity in plasma occurred at 8 hours (9 76 μg/ml) and at 24 hours in blood (6 52 μg/ml), with plasma and blood half lives of 2 3 and 4 8 days respectively Excretion was primarily in the feces (75%, 73% within one day) with 15 5% found in expired air and only 1% recovered in the urine. Residual radioactivity in the carcass at 168 hours was 4 3% Tissue analysis and autoradiography indicated that peak levels of radioactivity occurred at 8-24 hours in all tissues except fat, with the highest amounts found in pancreas, mandibular gland, spleen, liver, kidney and adrenals glands in descending order Tissue levels declined to levels comparable to blood levels in all organs/tissues examined by 168 hours with the exception of fat and spleen which had tissue concentrations approximately two-fold greater than blood levels These results indicate that ε-polylysine is poorly absorbed from the gastrointestinal tract and the absorbed compound(s) do not concentrate in any particular organ or tissue

The definitive absorption, distribution, metabolism and excretion studies were conducted at ADME/TOX Research Institute (ADME/TOX, 2001) Eighteen male rate were assigned to four experimental groups three rats to Group 1 for determination of radioactivity in blood and plasma, nine rats to Group 2 for determination of parent compound and low molecular weight compounds in plasma, three rats in Group 3 for determination of radioactivity in urine, feces, expired air and residual carcass, and three rats to Group 4 for whole body autoradiography Rats were fasted from 3 00 PM the previous day prior to dosing and given food 4 hours post-dosing Aqueous dosing solutions were formulated to contain 20 mg/ml ^{14}C-labeled ε-polylysine Rats were dosed orally by gavage with the volume calculated to deliver 100 mg/kg based on the individual animal body weights Animals used for blood and plasma collections were held as groups of three in standard caging Animals were held in glass metabolism cages with wire mesh bottoms for collection of urine, feces and expired air and cages were washed with distilled water to recover urine radioactivity Carbon dioxide in expired air was collected in dual traps containing 20% aqueous monoethanolamine Serial blood samples were taken from the tail vein in Group 1, animals in Group 2 were exsanguinated from the abdominal aorta The design of the ADME study is summarized in the following Table2 with collection times and biological samples taken

Table 2. Group Designations, Dose and Collections for ADME Study

Group	Number Animals (males)	Test Article Study Parameters	Target Dose (mg/kg)	Total Radio-activity (MBq/kg)	Collections *Matrix and Times* (hours post-dosing)
1	3	^{14}C-ε-polylysine Radioactivity in blood and plasma	100	3 7	Blood· 0-1, 1-2, 2-4, 4-6, 6-8, 8-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168
2	9	^{14}C-ε-polylysine Parent and metabolites in plasma	100	7 4	Blood 0-8, 8-24, and 24-72
3	3	^{14}C-ε-polylysine Excretion in urine, feces and expired air	100	3 7	Urine and CO_2 in expired air 0-4, 4-8, 8-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-Feces 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 Carcass. 168
4	3	^{14}C-ε-polylysine Whole body autoradiography	100	7 4	Whole body autoradiography 8, 24 and 168

Blood and plasma samples in Group 1 were dissolved in Soluene-350 tissue solubilizer (Packard) and decolorized with benzyl peroxide Plasma samples in Group 2 were processed by adding 1% ammonia water/methanol to plasma followed by sonication and centrifugation The supernatant was collected and the procedure was repeated twice more Urine samples from three animals were combined and diluted with distilled water for scintillation counting or evaporated to dryness and reconstituted in solvent for HPLC analysis Combined fecal samples from all animals in a group were homogenized prior to centrifugation to separate the fecal-bound from free radioactivity prior to radiation counting Samples were then added to scintillation solutions or analyzed by HPLC as appropriate For whole body autoradiography, animals were frozen in dry ice-acetone and 35 μm frozen sections were prepared Sections were covered with a protective membrane and stored on imaging plates (TYPE-BAS, Fuji Film) The radioactive images were analyzed by a Bio-image device (FUJIX BAS2000, Fuji Film) to prepare color radiolumigrams

Data on absorption and elimination of radioactivity from the blood and plasma pool following oral administration of 100 mg ^{14}C-labeled ε-polylysine is presented in Table 3 Because all carbons were radiolabeled, these data do not necessarily show the presence of ε-polylysine, but reflect the radioactivity concentrations equal to microgram

equivalents (μg eq) of labeled ε-polylysine carbons The t_{max} in blood was 7 3 hours, and in plasma, 8 0 hours, suggesting a slow or delayed absorption of radioactivity The C_{max} concentrations estimated for blood and plasma were 3 158 and 5 134 μg eq ε-polylysine/ml, which occurred 6-8 hours post-dosing Half-lives for elimination from blood and plasma over the 72-168 hour period were prolonged to 20 and 3 9 days, respectively, reflecting the incorporation of L-lysine into protein. Less than half of the peak radioactivity (5 134 μg eq ε-polylysine/ml) in plasma at 8 hours was found in plasma at 48 hours (2 225 μg eq ε-polylysine/ml), but the blood radioactivity at termination (168 hours) had not declined to half the 8 hour peak Interestingly, area-under-the-curve (AUC) values for blood and plasma for the 0-168 hour period were practically the same

Table 3. Concentration of Radioactivity in Blood and Plasma of ε-Polylysine Equivalents

Time	Radioactivity concentration (μg eq of ε-polylysine/ml)	
	Blood	Plasma
30 min	N D	0 240 ± 0 014
1 hr	0 337 ± 0 059	0 499 ± 0 061
2	1 014 ± 0 079	1 456 ± 0 144
4	2 438 ± 0 247	3 848 ± 0 535
6	3 039 ± 0 728	4 994 ± 1 339
8	2 963 ± 1 089	5 134 ± 1 240
24	2 273 ± 0 548	3 277 ± 0 815
48	2 169 ± 0 565	2 225 ± 0 498
72	2 079 ± 0 496	1 843 ± 0 464
96	1 844 ± 0 392	1 464 ± 0 362
120	1 817 ± 0 426	1 244 ± 0.257
144	1.808 ● 0 388	1 010 ± 0.317
168	1 716 ± 0 286	0 908 ± 0 163
Detection limit	0 178	0 198
t_{max} (hr)	7 3 ± 1 2	8 0 ± 0.0
C_{max} (μg eq /mL)	3 158 ± 0 889	5 134 ± 1 240
$t_{1/2}$ (72-168hr) (day)	20 ± 6	3 9 ± 0 4
AUC (0-168hr)	339 ± 79	330 ± 78
(μg eq hr/ml) (0-∞)	1470 ± 270	453 ± 87

Data are expressed as the mean values ± S D of three animals

N D Not detected

The cumulative excretion of radioactivity in urine, feces and expired air, as well as residual activity in the carcass, is presented in Table 4 The overall mean recovery from all routes and biological samples was approximately 100% of the administered radioactivity The great majority of the radioactivity was recovered in the feces within the first 24 hours (71 5%), by 48 hours, 92 9% of the dose was found cumulatively in the feces and practically all subsequent elimination in the feces was complete by 72 hours In expired air, approximately 50% of the total cumulative amount (3 4%) over the 168 hour collection period was captured within the first 8 hours and approximately 90% of the total within 48 hours (3 0%) Little radioactivity was found in the urine for the first 8 hours By 48 hours, 1 2% or 57% of the cumulative collection was excreted, through 168 hours, the cumulative radioactivity in the urine totaled 2 1% of the dose administered The residual carcass had only 0 9% of the dose and amounts recovered by cage washing were minimal

As these data show, the entire dose of radioactivity was eliminated by excretion within 168 hours and over 97% was accounted for in urine, feces or expired air by 48 hours, mainly in the feces (92 9%) The sum of the cumulative excretion with routes associated with absorption, urine, expired air and carcass, is 6.4% of total recovered radioactivity Therefore, the results of the excretion study clearly demonstrate that approximately 94% of the dose of ε-polylysine passed unabsorbed through the gastrointestinal tract and was eliminated in the feces

Table 4. Cumulative Excretion of Radioactivity in Urine, Feces and Expired Air

Time (hr)	Excretion of Radioactivity (% of dose)			
	Urine	Feces	Expired Air	Total
0 - 4	0 0 ± 0 0	–	0 3 ± 0 1	–
8	0 1 ± 0 1	–	1 7 ± 0 7	–
24	0 8 ± 0 7	71 5 ± 11 6	2 6 ± 0 8	75 0 ± 12 9
48	1 2 ± 0 7	92 9 ± 0 8	3 0 ± 0 8	97 1 ± 0 8
72	1 5 ± 1 0	94 1 ± 1.5	3 1 ± 0 9	98 7 ± 0 2
96	1 7 ± 1 1	94 2 ± 1 5	3 2 ± 0 8	99 1 ± 0 4
120	1 9 ± 1 2	94 3 ± 1 5	3 3 ± 0 8	99 5 ± 0 5
144	2 0 ± 1 3	94 4 ± 1 5	3 4 ± 0 9	99 7 ± 0 7
168	2 1 ± 1 5	94 4 ± 1 5	3 4 ± 0 9	100 0 ± 0 9
Carcass (168 hr)				0 9 ± 0 1
Cage washing (168 hr)				0 0 ± 0 1

Data are expressed as the mean values ± S D of three animals

– Not determined

A follow-up metabolism study was conducted in order to characterize the metabolic by-products in plasma and feces (Tokai Research, 1995b) Following gavage dosing of a male rat at 100 mg/kg ^{14}C labeled ε-polylysine, blood was collected at 30 minutes and 4 and 8 hours after dosing, feces were collected from 0-24 hours Samples were extracted with methanol and put through high performance liquid chromatography (HPLC) to separate the radioactivity into fractions related to their molecular weight Control sample recoveries from plasma were reduced over time, reported as 83%, 25% and 20% at 30 minutes, 4 and 8 hours respectively (Hiraki *et al.*, 2003)

Using polylysine, 4 mer and 6 mer synthesized to serve as comparative control compounds, only the 4 mer was found present in plasma (0 006 μg/ml, 0 8% of total radioactivity in plasma) at 30 minutes post-dosing above the limit of detection At 4 hours, neither polylysine nor its polymer fragment degradation by-products were noted in plasma At eight hours, plasma levels of the 6 mer were 0 033 μg/ml (0 6% of total radioactivity) and polylysine, 0 012 μg/ml (0 2% of plasma radioactivity), with no 4 mer being detectable These results indicate that less than 1% of the absorbed radiolabel was in the form of polylysine or polymeric fragments such as the 4 or 6 mer With the great majority of the recovered plasma counts having longer HPLC retention times than polylysine or the polymeric 4 mer or 6 mer fragments, it was apparent that the plasma metabolites were of shorter chain length In the feces, 0 7% (1% of total plasma counts) of administered dose was recovered as polylysine, 0 3% (0 5%) as 4 mer and 1 9% (2 8%) as the 6 mer over the 24-hour collection period Because only 8% of radioactivity could be recovered in the supernatant of centrifuged feces, most of the polylysine or its metabolites were considered to be bound to the fecal solids (Hiraki *et al.*, 2003)

The metabolic profile of ε-polylysine was further investigated by administering radiolabelled ^{14}C-L-lysine at 100 mg/kg to male rats by gavage and collecting blood samples at 30 minutes and 4 hours (Tokai Research, 1996) Plasma samples were extracted with methanol for HPLC analysis, recoveries of radioactivity from samples were 77 6% and 9 4% for the 30 minute and 4 hour samples respectively At 30 minutes, 67 2% of the radioactivity in plasma corresponded to L-lysine (48 7 μg/ml) and at 4 hours, 7 5% of the radioactivity appeared to be L-lysine These data suggest that absorbed L- lysine is readily incorporated into protein or further metabolized (Hiraki *et al.*, 2003)

Earlier reports have shown that lysine is degraded to α-aminoadipate through the saccharopine intermediate in rat liver mitochondria (Higashino *et al*, 1967, Grove *et al*, 1970) Studies of L-lysine catabolism in guinea pigs and rats have also shown the presence of α-aminoadipate, which is deaminated to another reported metabolite, α-ketoadipate in these animals (Rodwell, 1969) Therefore, a reasonable interpretation is that the metabolism of ε-polylysine proceeds primarily by cleavage of L-lysine amino acid from the homopolymer with slight 4 mer and 6 mer fragment formation. The L-lysine is further degraded to the α-aminoadipate and α-ketoadipate metabolites that are each found in plasma at levels comparable to L-lysine at 4 hours It is possible that both gut microflora and the liver are capable of degrading L-lysine and contributing to the α-aminoadipate and α-ketoadipate metabolites found in plasma

Acute Toxicity Study

Young Sprague-Dawley rats (10/sex/dose group) were administered 10% ε-polylysine in water at dose levels of 1 25, 2 5 and 5 g/kg by gavage (Life Science, 1989). With the exception of a slight depression in spontaneous activity in rats dosed at 5 g/kg at 5 minutes, which returned to normal at 3-6 hours, no clinical signs of toxicity were observed No differences in weight gain were found related to treatment during the fourteen-day observation period nor did any deaths occur At necropsy, there were no abnormal findings in any major organ Therefore, the acute oral LD_{50} was greater than 5 g/kg or practically non-toxic by the oral route (Hiraki *et al.*, 2003)

Subchronic and Chronic Toxicity Studies

A subchronic oral toxicity study in rats was conducted by continuous dietary administration to Sprague-Dawley rats (Ishii *et al*, 1993) Groups of ten rat/sex were given diets containing 2,000, 10,000 and 50,000 ppm ε-polylysine in the diet for 90 days This corresponded to a mean daily intake for males or females respectively of 179 or 193, 895 or 995 and 4295 or 4779 mg/kg at the low, mid and high dose Body weight and food consumption was measured weekly and general animal condition was monitored daily At termination, standard urinalysis and hematological analysis including leukocyte analysis and prothrombin time were conducted An extensive series of biochemical indicators, enzymes and electrolytes were evaluated in the blood clinical chemistry studies Following gross observations of the organs, organ weights were taken on the liver, kidneys, brain, pituitary, thyroid, submaxillary gland, thymus, heart, spleen, adrenals, testes, seminal vesicle, prostate, uterus and ovary In addition to these organs, numerous other tissues were collected for subsequent histopathological examination.

At 50,000 ppm, male and female rats showed significant decreases in food consumption beginning at weeks 1-5 and significant depression of weight gain from the first week of treatment The reduction in weight gain was attributed to the poor palatability of the bitter tasting polylysine resulting in reduced food intake. No significant decrease in weight gain, food or water consumption were seen at 10, 000 ppm and below Rats of both sexes had decreased potassium excretion at the high dose, with females also having reduced volume and increased specific gravity Urinalysis was unaltered by treatment in the lower dose groups

Male rats at 50,000 ppm had significant decrease in leukocyte count and increase in segmented leukocyte ratio In the lower dose groups, sporadic changes in hematocrit, mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin and lymphocyte or segmented lymphocyte ratios were noted The hematological changes in all treatment groups were not considered to be of toxicological significance since they were not dose dependent, were slight in magnitude and within the historical ranges for controls Further, no histopathology was seen in any part of the hematopoeitic system including spleen, bone marrow, lymph ducts and thymus gland Males and females showed significant decreases in blood glucose, total protein, albumin, triglyceride and phospholipid levels and male rats had lowered cholesterol These changes were thought to be secondary to reduced food consumption Other groups had sporadic, non dose-

dependent changes in biochemistry parameters that were considered to be within historical ranges and not toxicologically significant

Due to the reduced weight gain seen in the high dose group males and females, several organ weights were found to be reduced on an absolute basis relative to controls The relative organ weights were reduced only for the liver in mid and high dose males and females and for the thyroid in all female treatment groups With the exception of a diffuse slight atrophy of hepatocytes in animals treated at 50,000 ppm, no histopathological abnormalities related to treatment were observed in any dose group Based on the findings in this subchronic feeding study, the no-observed-adverse effect-level was considered to be 10,000 ppm in the diet (895 mg/kg in males and 995 mg/kg in females)

Following the subchronic study, a chronic oral toxicity and carcinogenicity study in rats was conducted by continuous dietary administration to Sprague-Dawley rats (Fukutome *et al* , 1995) Groups of 80 rat/sex were given diets containing 2,000, 6,500 and 20,000 ppm ε-polylysine in the diet for 102-104 weeks This corresponded to a mean daily intake for males or females respectively of approximately 100 or 122, 332 or 417 and 1060 or 1317 mg/kg at the low, mid and high dose Body weight and food consumption was measured weekly through week 14 and monthly thereafter General animal condition was monitored daily and palpable masses were noted and measured weekly after week 26 For ten rats/sex/group, at every thirteen weeks during the study and on all survivors at termination, standard urinalysis and hematological analysis including leukocyte analysis and prothrombin time were conducted An extensive series of biochemical indicators, enzymes and electrolytes were evaluated in the blood clinical chemistry studies, also on ten rats/sex/group, at every thirteen weeks during the study and on all survivors at termination Following gross observations of the organs, organ weights were taken on the liver, kidneys, brain, spleen, adrenals and testes on weeks 26, 52 and 78 for 10 rats/sex/group as well as all survivors at termination. In addition to these organs, numerous other tissues were collected for subsequent histopathological examination at these time points

Due to the bitterness of ε-polylysine in the diet, there was reduced feed intake in the high dose males and females through the middle of the study, which was associated with reduced weight gain through that period At termination, the body weights were not significantly different between treated and control groups No significant reduction in body weight was seen in the lower dose groups at any time No increased incidence of abnormal clinical signs or reduced survival was observed Although sporadic alterations of some parameters were found, no changes in hematology, blood biochemistry or urinalysis were seen that were considered treatment related differences Gross observations and organ weights were unremarkable Similarly, the non-neoplastic and neoplastic lesions observed in treated and control animals did not show dose-dependent increases and were considered to be spontaneous in origin Based on the results of this study, ε-polylysine up to 20,000 ppm (1060 or 1317 mg/kg in males or females respectively) in the diet did not result in any adverse effects other than reduced weight gain in high dose animals through mid-study which reverted to normal body weight by

termination, the reduced weight gain was likely due to poor diet palatability from the bitter test agent and reduced early stage feed intake

Genetic Toxicity

ε-Polylysine was tested for mutagenicity in the Ames/*Salmonella* tester strains TA1535, TA 1537, T98 and TA100 and *Escherichia coli* WP2 uvrA with and without S-9 metabolic activation (BML, 1995) When tested up to 5 μg/plate in *Salmonella* strains and up to 20 μg/plate in *E coli*, ε-polylysine did not induce any significant or dose-responsive increase in revertants indicative of mutagenic activity (Hiraki *et al.*, 2003)

Antibacterial Presence Study

ε-Polylysine molecules are cationic, surface active agents due to their positively charged amino groups in water They have hydrophobic methylene groups on the inside and hydrophilic carboxyl and amino groups on the outside of the molecule in polar solutions Cationic surface-active compounds generally inhibit the proliferation of microorganisms and ε-polylysine has been shown to have antimicrobial properties

Actinomycetes such as *Streptomyces albulus* are known to produce multiple antibacterial substances besides ε-polylysine In order to assure that other antibacterial substances were not present in the ε-polylysine product, a study was conducted to identify and detect other antibacterials that may be present in the final product (Chisso, 2001) The fermentation product was fractionated on silica gel after removal of polylysine and tested on paper discs against *Bacillus cereus*, *Escherichia coli* and *Staphyloccus aureus*. Two fractions, designated fraction A and B were found to have zones of inhibition on agar plates demonstrating antibacterial activity A minimal inhibitory concentration was determined for both fractions, approximately 0 25% w/w for *B cereus* and *S aureus* for both fractions The fractions were then run on a high-pressure liquid chromatograph (HPLC) to determine peak retention times After admixture with polylysine fractions, the limits of detection were determined to be 1 1 μg/ml for fraction A and 0 045 μg/ml for fraction B When the ε-polylysine purified product was run through HPLC analysis, neither fraction A nor fraction B was detected Therefore, the presence of these fractions was considered negligible being less than 0 053% and 0 011% or less of the product respectively These levels are well below the 0 25% w/w amounts found to be necessary for antibacterial activity

Another indicator of potential antimicrobial activity of ε-polylysine and minor antibacterial fractions A or B would be alterations in the gastrointestinal tract of animals fed the ε-polylysine product in the diet for a lifetime If the antimicrobial activity of these compounds were sufficient to affect the normal gut microflora *in vivo*, it is typical for rats to exhibit cecal enlargement In neither the subchronic nor chronic feeding studies were there any indications of treatment-related pathological changes in the gastrointestinal tract indicative of a substantial change in the gut microflora

Allergenic Potential

No reports were found in the literature of any allergenic reactions or any other adverse effects associated with the use of ε-polylysine in food, even with common use in Japan The structure of ε-polylysine is not typical of proteinaceous compounds in that it consists of a polymer with only single amino acid constituent versus the normal presence of multiple different amino acids in protein molecules Further, the amide linkage is not between the alpha-amino and carboxyl groups as in a peptide bond but between the ε-amino and the carboxyl group

Discussion

ε-Polylysine is approved by the Japanese authorities for food additive use as an antimicrobial preservative It has a history of safe use in several staple foods of their diet including boiled rice, traditional dishes, sukiyaki, noodle soup stocks, noodles and cooked vegetables. There are no reports of adverse effects in the literature associated with the food use of ε-polylysine

Pharmacokinetic and metabolism studies have shown that ε-polylysine itself is practically non-absorbed into systemic circulation, constituting approximately 0 2% of recovered label in plasma at the 8 hr time point only The radioactivity found in the pharmacokinetic studies is associated with L-lysine that has been cleaved from the homopolymer and likely further metabolites, α-aminoadipate and α-ketoadipate, which are the normal endogenous byproducts of lysine amino acid metabolism As noted before, the intake of lysine from a protein meal would be several hundred times that associated with any potential release from the ε-polylysine polymer Therefore, even though intake of ε-polylysine may be as high as 15 mg/day, systemic absorption of polylysine or fragments larger than the lysine amino acid are likely to be less than 2% of the total intake

ε-Polylysine was practically non-toxic in an acute oral study in rats and was non-mutagenic in bacterial assays A study conducted to determine the presence of other antimicrobial compounds in the ε-polylysine product has demonstrated that their presence is negligible Long-term animal studies have shown no characteristic changes such as cecal enlargement associated with alterations in gut microflora from antimicrobial activity of ε-polylysine or any other antibacterial residues The structure of ε-polylysine is not similar to sequences found in other protein allergens and is considered unlikely to have an allergenic potential This is reinforced by the lack of any reported untoward effects even with extensive human exposures

ε-Polylysine has been the subject of subchronic and chronic toxicity or carcinogenicity studies by dietary feeding in rats Reduction in body weight and organ weights associated with poor diet palatability and mild liver changes were observed in the subchronic study at the high dose of 50,000 ppm (4295 mg/kg/day) In the chronic toxicity/carcinogenicity study, rats given 20,000 ppm ε-polylysine in the diet had reduced body weight from poor palatability through the middle of the study term, but recovered to

control body weight values by the end of the study Neither the liver or any other organ or tissue showed a treatment-related effect at any dose level by histopathological examinations No consistent or dose-related alteration of clinical biochemistry, urinalysis or hematology was associated with treatment in the chronic feeding study Based on the results of the chronic study and the absence of toxicological effects in any dose level, the no-observed-adverse-effect-level (NOAEL) is considered to be 20,000 ppm in the diet or 1060 mg/kg which was the lower value ingested by the male rats than 1317 mg/kg in high dose females

Pharmacokinetic and metabolism studies have shown that ε-polylysine and its metabolites formed in the gastrointestinal tract are minimally absorbed into systemic circulation In the cumulative excretion study, approximately 94% of the radioactivity was unabsorbed and excreted in the feces, the great majority within 48 hours. As seen in the molecular weight studies, the low recoveries (8 3% and 4 9%) of radioactivity in the supernatant as a percent of total activity in fecal homogenates indicate that water-soluble ε-polylysine and its metabolites are bound to the fecal solids Binding of ε-polylysine to feces may partially account for its poor absorption Of the remaining 6% excreted by routes that involved absorption, 3 4% was released as $^{14}CO_2$ in expired air, 2 1% was found in urine and 0 9% remained in the carcass Whole body autoradiography also demonstrated that orally administered ε-polylysine and metabolites remain primarily in the stomach and intestinal tract and do not concentrate in any tissue or organ By 168 hours, only trace levels of radioactivity were found in the tissues and organs by autoradiography and image analysis

The absorption of radioactivity from the stomach and upper intestinal tract as expressed in μg eq /ml of ε-polylysine was relatively slow with the maximum concentrations in blood and plasma occurring at 8 hours at relatively low levels in the range of 3 to 5 μg eq /ml Although the plasma values declined over 50% from the 8 hour peak values within 40 hours, longer half-lives of 3 9 days were calculated for plasma and 20 days for blood, based on the 72-168 hour concentrations The most likely explanation for these prolonged half-lives is that a significant proportion of the early blood and plasma radioactivity is from absorbed L-lysine amino acid cleaved from ε-polylysine by proteases in the upper intestinal tract These proteases may be produced by bacteria in the gastrointestinal tract, a ε-polylysine-degrading hydrolytic enzyme has been purified and characterized from *Sphingobacterium multivorum* (Kito et al , 2002). Upon absorption, L-lysine is readily incorporated into longer-lived peptides and proteins, which are released and persist in circulation Detailed analysis of HPLC profiles from the metabolic studies support this interpretation (Hiraki *et al* , 2003)

Assuming a worst-case maximum usage of ε-polylysine of 50 ppm in boiled rice and a daily intake of 15mg/day that is completely absorbed, the daily intake for a 60 kg person would be 0 25 mg/kg In comparison to the rat chronic NOAEL of 1060 mg/kg, there is a margin of safety for the proposed use of over 4000 fold A safety factor of 100 from chronic animal studies is generally considered acceptable for use of a food additive Therefore, even with worst-case assumptions, a sufficient margin of safety is present for the proposed use of ε-polylysine as an antimicrobial food additive

GRAS Panel Statement and Conclusion

Based on a critical evaluation of the above data and information, the Expert Panel has determined that ε-polylysine, meeting the specifications cited above, is generally recognized as safe (GRAS) by scientific procedures when used as an antimicrobial ingredient in rice and sushi rice at levels up to 50 ppm.

Douglas Archer, Ph.D. — Date 7/8/03

W Gary Flamm, Ph.D., FACT, FATS — Date 7/3/03

Donald A. Hughes, Ph.D. — Date 7/7/03

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Tokai Research (1995b) Pharmacokinetic studies of polylysine (II) Metabolism in rats Tokai Research Laboratories Study Number AE-2229

Tokai Research (1996) Pharmacokinetic studies of polylysine (III) Metabolism in rats. Tokai Research Laboratories Study Number AE-2317

USDA (1989-1991) Continuing Survey of Food Intake by Individuals U S Department of Agriculture, Washington, DC

Attachment 1

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CURRICULUM VITAE

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EDUCATION:

Doctor of Philosophy (Biological Chemistry, University of Cincinnati, Cincinnati, Ohio, 1959-1962.

Master of Science (Pharmaceutical Chemistry), University of Cincinnati, Cincinnati, Ohio, 1957-1959.

Bachelor of Science (Pharmacy), University of Cincinnati, Cincinnati, Ohio, 1953-1957.

PROFESSIONAL POSITIONS:

Consultant, Flamm Associates, 1988-present.

Director, Office of Toxicological Sciences, Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration (US FDA), 1984-1988.

Associate Director for Toxicological Sciences, Bureau of Foods, US FDA, 9/82 - 3/84.

Acting Associate Director for Toxicological Sciences, Bureau of Foods, US FDA, 5/82 - 9/82.

Acting Associate Director for Regulatory Evaluation, Division of Toxicology, Bureau of Foods, US FDA, 10/81 - 5/82.

Deputy Associate Commissioner for Health Affairs, US FDA, 5/81 - 10/81.

Acting Deputy Associate Commission for Health Affairs, US FDA, 7/80 - 7/81.

Associate Director for Regulatory Evaluation, Division of Toxicology, Bureau of Foods, US FDA , 11/78 - 7/80.

Assistant Director for Division of Cancer Cause and Prevention, National Cancer Institute, NCI, 9/74 - 10/77.

Chief, Genetic Toxicology Branch, Bureau of Foods, US FDA, 9/72 - 9/74.

Head, Somatic Cell Genetics Section, National Institute of Environmental Health Sciences, National Institutes of Health, 1/72- 9/72.

Research Chemist, Cell Biology Branch, National Institute of Environmental Health Sciences, National Institute of Health 6/68 - 1/72.

Sr. Research Fellow, Dept. of Zoology, University of Edinburgh, Edinburgh, Scotland, 9/66 - 7/68.

Research Chemist, National Cancer Institute, National Institute of Health, 7/64 - 9/66.

Research Fellow, California Institute of Technology, 6/62 - 7/64.

Predoctoral Fellow, Department of Biochemistry, University of Cincinnati, 9/59 - 6/62.

PROFESSIONAL SOCIETIES AND HONORS:

Fellow, Academy of Toxicological Sciences, 1999 -present

American College of Toxicology (Charter Member) 1977-present
- President, 1984-1985
- Fellow of the American College of Toxicology, since 1986
- Chairman, Program Committee 1983, 1984
- Membership Committee, 1979, 1981
- Program Committee, 1984-1985
- Nominee Committee, 1982-1983
- Council, 1982-1984
- Publications Committee, 1983-1984

Environmental Mutagen Society (EMS) (Charter Member) 1969-present
- Treasurer, 1973-1974
- Council, 1974-1976, 1978-1981

Executive Board, 1975-1976
Chairman, Program Committee, 1974
Chairman, Nomination Committee, 1978-979
Finance Committee, 1979-1980
Long-Range Planning Committee, 1979-1980

Society for Risk Analysis (Charter Member & Co-Founder) 1980-present
Secretary 1992-1997
Council 1988-1990
Program Committee, 1981-1982
President's Advisory Committee, 1981-1982
Membership Committee, 1988-1990

International Society for Regulatory Toxicology and Pharmacology, 1985-present
President, 1990-1992
Vice President, 1988-1990

The Toxicology Forum
Member 1992-present
Program Planning Committee – 1980-1994

Sigma Xi

Member, Federal Executive Institute Alumni Association, 1982

Former Member, American Chemical Society, Genetics Society of America,

Former Biophysical Society, American Pharmaceutical Association, Biochemical Society,

Former American Association for the Advancement of Science, New York Academy of Science, American Forestry Association

George Scott Memorial Award, Toxicology Forum, 1988

U.S. FDA Senior Executive Performance Award for Outstanding Performance during fiscal years 1980, 1982, 1983, 1984

Environmental Mutagen Society's Recognition Award, 1981. "For his accomplishments both in research and the administration of toxicology programs, especially for his untiring efforts to establish genetic toxicology as an essential component of chemical safety evaluation."

U.S. Department of Health, Education and Welfare Superior Service Award, 1977. "For vigorous leadership in reshaping the philosophy and methods for assessing environmental carcinogenic hazard to humans on a national and international scale.

Elected Class Representative to Senior Executive Training Program, 1980

U.S. Public Health Service Predoctoral Fellowships, 1962, 1963, 1964

Sigma Xi - honorary graduate

U.S. Public Health Service Predoctoral Fellowships, 1959, 1960, 1961, 1962

Rho Chi - honorary Pharmaceutical Society, 1958

Otto Mooseburger Award in Pharmacy, 1957

ADDITIONAL TRAINING:

Radiation Biology, University of Sao Paulo, Brazil, 1971

Molecular Biology, University of Edinburgh, Scotland, 1966-1968

Biochemical Genetics, National Institutes of Health, 1965-1966

Molecular Biology, Biophysics, California Institute of Technology, Pasadena, California, 1962-1964

Senior Executive Training Program, Federal Executive Institute, 1980

COMMITTEES, CHAIRMANSHIPS AND RESPONSIBILITIES:

Special Foreign Assignment to the University of Edinburgh, Edinburgh, Scotland, 1967-1968

Testimony before US Senate on "Chemicals and the Future of Man," 92nd Congress, Subcommittee on Executive Reorganization and Government Research, Washington, D.C., 1971

Organizer and Chairman "Methods for the Detection of Somatic Mutations in Man," NIEHS/NIH, Research Triangle Park, North Carolina, 1972

Executive Secretary - Subcommittee on Carcinogen Laboratory Standards, DHEW, 1973-1975

Chairman - Subcommittee on Carcinogenicity of NTA, Committee to Coordinate Toxicology and Related Programs, DHEW, Bethesda, Maryland, 1974-1975

Executive Secretary - National Cancer Advisory Board Subcommittee on Environmental Carcinogenesis, Bethesda, Maryland, 1975-1977

Chairman - Working group to develop document on "Approach to Determining the Mutagenic Properties of Chemical Substances," CCTRP, DHEW, 1975-1977

Preparation of testimony and hearing statements before NIH appropriation subcommittees of the Congress on cancer prevention for the National Cancer Institute, 1975, 1976

Preparation of testimony and appearance before U.S. Senate Health Subcommittee on Diethylstilbestrol Hearings, 1975

Member, DHEW Subcommittee on polychlorinated biphenyls, Bethesda, Maryland, 1975
Coordinated and participated in the interdepartmental HEW study on the toxicology and health effects of polybrominated biphenyl, 1975-1977

Chairman, Carcinogenesis Coordinating Committee, National Cancer Institute, Bethesda, Maryland, 1976-1977

Member of the FDA interagency committee to evaluate carcinogenicity of FD&C Red No. 40, Washington, D.C., 1976-1978

Testimony before a U.S. Congress on saccharin, House Health Subcommittee, 1977

Commissioner's Task Force on the 1977 National Academy of Sciences report on the National Center for Toxicologic Research, Rockville, Maryland, 1977-1978

Chairman, Cancer Assessment Committee, FDA/Bureau of Foods, Washington, D.C., 1978-1988

Chairman, Mutagenicity Working Group on Risk Evaluation, U.S. Environmental Protection Agency, 1978-1980

Chairman, Health Effects of Diesel Fuel Emission, U.S. Environmental Protection Agency, 1978

Testimony before U.S. House of Representatives, Committee on Science and Technology on Use of Animals in Medical Research and Testing, 1981

Member of Working Group on methods for the integrated evaluation of risks for progeny associated with prenatal exposure to chemicals - WHO/International Program for Chemical Safety 1981

Working Group on Carcinogen Principles, White House Office of Science Technology Policy, 1982

Testimony before a U.S. House of Representatives, Committee on Science and Technology, hearing on Hazards of Chemicals to Human Reproduction, 1982

Member, Risk Management Working Group, Interagency Risk Management Council, 1984, 1985

Co-chairman, U.S. FDA, Health Hazard Evaluation Board,1982-1988

Chair, Session on Mutagenesis, Annual Meeting of the American College of Toxicology, 1980

Chairman, Food and Risk Assessment, *Mechanisms of DNA Damage and Repair:* Implications for Carcinogenesis and Risk Assessment, 1985

Chair, Session on DeMinimus Risk, International Society of Regulatory Toxicology and Pharmacology, 1987

Chairman, Approaches to Validation, In Vitro Toxicology, sponsored by the Johns Hopkins Center for Alternatives to Animal Testing, 1986

Chair, Risk Analysis and the Food and Drug Administration, Society for Risk Analysis, Annual Meeting, 1988

Chair, Risk Assessment in the Federal Government: Managing the Process, Toxicology Forum, 1983

Chair, Program Committee, Annual Meeting of the International Society of Regulatory Toxicology and Pharmacology, 1987, 1988, 1989

Chair, Risk Assessment, Toxicology Forum, 1990

Ad Hoc Chair of Expert Panels on Generally Recognized as Safe Substances from

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FACULTY APPOINTMENTS:

Adjunct Associate Professor, Department of Zoology, University of North Carolina, Chapel Hill, North Carolina, 1968-1972

Visiting Professor of Biochemistry, University of Sao Paulo, Brazil, 1970 and 1971

Adjunct Professor of Genetics, George Washington University, Washington, D.C., 1972-1974

Visiting Professor, European Molecular Biology Organization, University of Zurich, Zurich, Switzerland, 1973

Visiting Professor, University of Conception, Chile, 1979

EDITORIAL AND ADVISORY ACTIVITIES:

Manuscript review for numerous journals, e.g., Biochem. Biophys. Acta, Science, Proc. Natl. Acad. Sci., J. Mol. Biology, J. Biochem, Genetics, Biochemical Journal, Expt. Cell Research, Cancer Research, J. Natl. Cancer Institute, Mutation Research, Radiation Research, Food and Chemical Toxicology, J. Toxicology and Environ. Health, Genetic Toxicology, CRC Reviews in Toxicology

Associate Editor, Journal of Environmental Health and Toxicology, 1974-1978

Section Editor, Journal of Environmental Pathology and Toxicology, 1978-1982

North American Field Editor, Teratogenesis, Carcinogenesis and Mutagenesis, 1994-present

Editorial Board, Genetic Toxicology, 1975-1978

Editorial Board, Food and Chemical Toxicology, 1977-1988

Editorial Board, Biomedical and Environmental Sciences, 1988-present

Sec. Ed., Journal of the American College of Toxicology, 1982-1996

Member of Editorial Board, Journal for Risk Analysis, 1982-1986

Member of Editorial Board, Regulatory Toxicology and Pharmacology, 1986-present

Co-editor, Advances in Modern Toxicology: Mutagenesis, 1976-1978

Co-editor, Carcinogenesis & Mutagenesis, Princeton Scientific Publishers, 1979-1981

Member, Genetics Program Committee, George Washington University, Washington, D.C., 1972-1975

Member, Joint Subcommittee on Mutagenicity, Pharmaceutical Manufacturers Association - Food and Drug Administration, Washington, D.C., 1972-1974

Member, Faculty Group, European Molecular Biology Organization, Geneva, Switzerland, 1973

Member, US/USSR Delegation to Moscow, Environmental Health Agreement, DHEW, 1974

Member, Scientific Advisory Board, National Center for Toxicological Research (NCTR), Jefferson, Arkansas, 1975-1978

Chairman, Subcommittee on Mutagenesis, Science Advisory Board, National Center for Toxicological Research, Jefferson, Arkansas, 1975-1978

Chairman, Subcommittee on Genetic and Environmental Influences on Carcinogenesis (matrix) Sci. Adv. Board, National Center for Toxicological Research, Jefferson, Arkansas, 1975-1978

Member, Toxicology Advisory Committee, Food and Drug Administration, Rockville, Maryland, 1975-1978

Member, National Academy of Sciences, Committee to Develop Principles for Evaluating Chemicals in the Environment, Washington, D.C., 1975

Chairman, Subcommittee on Tissue Culture Resources, Sci. Adv. Board, National Center for Toxicologic Research, Jefferson, Arkansas, 1976-1978

Member, National Academy of Sciences Committee to Revise Publication No. 1138, Toxicologic Evaluation of Household Products, Washington, D.C., 1976-1977

Chairman, Subcommittee on Mutagenesis of NAS committee to revise Publication No.

1138, Washington, D C., 1976-1977

Member, National Academy of Sciences Visiting Committee to Review the Food and Nutrition Board, Washington, D.C., 1976-1977

Consultant, Organization of American States, Office of Scientific Affairs, Sao Paulo, Brazil, 1971.

Consultant, National Science Foundation, Structure and Function of Human Chromosome, Washington, D.C., 1971.

Advisor, National Science Foundation, Developmental Biology - Cell Biology, Washington, D.C., 1971-1972, 1978.

Consultant, World Health Organization, consultant group on anti-schistosomal agents, Geneva, Switzerland, 1972

Consultant, National Cancer Institute, Carcinogenesis Program, Bethesda, Maryland, 1972-1974

Consultant, Environmental Protection Agency, Washington, D.C., 1972-1973, 1976-1977

Consultant, Bureau of Drugs, Safety Evaluation, Rockville, Maryland, 1972-1974

Consultant, Consumer Product Safety Commission, 1973-1975, 1977

Consultant, National Institute on Drug Abuse, Rockville, Maryland, 1976-1977

Member, Faculty Group - International Course on Methods for the Detection of Environmental Mutagens, Concepcion, Chile, 1979

Chairman of the FDA's Recombinant DNA Coordinating Committee, 1980-1981

Co-Chairman Joint Committee on Agency-Wide Quality Assurance Criteria (FDA), 1980-1981

Chairman, Scientific Advisory Research Associates Program (FDA), 1980-1981

Chairman, International Visiting Scientific Program (FDA), 1980-1981

Chairman, Agency-Wide Research Review and Planning Group (FDA), 1981

Ex-Officio Member National Cancer Advisory Board, 1980-1981

Member, Interagency Regulatory Liaison Group on 1-Mutagenesis; 2-Cancer Risk, 1979-1981

Organizing Committee for First World Congress on Toxicology and Environmental Health, 1983

Organizing Committee for "Symposium on Health Risk Analysis", 1981

Chairman, Toxicology Committee, National Conference for Food Protection, 1985-1986

Member, NAS Committee on Biomedical Models, 1983-1985

INVITED PRESENTATIONS:

"Kinetics of Homogentisate Oxidase", Federation of American Societies of Experimental Biology, Atlantic City, New Jersey, 1961

"Histone Synthesis", invited speaker, First International Conference on Histone Chemistry and Biology, Santa Fe, California, 1963

"Free and Bound Ribosomes", FASEB, Chicago, Illinois, 1963

"Histone Synthesis" Seminar, California Institute of Technology, Pasadena, California, 1963.

"Association and Dissociation of RNP particles" Seminar, University of Cincinnati, Cincinnati, Ohio, 1963.

"Ribosome Synthesis", California Institute of Technology, Pasadena California, 1964.

"Protein and Nucleic Acid Biosynthesis", University of California, Santa Barbara, California, 1964.

Biosynthesis and Assembly of Ribosomes", Dupont Laboratories, Wilmington, Delaware, 1964.

"Isopycnic Density Gradient Centrifugation", University of Pennsylvania, Institute for Cancer Research, Philadelphia, Pennsylvania, 1965.

"Use of fixed-angle rotors" Seminar, Carnegie Institution of Washington, Washington, D.C., 1965.

"Conversion of 23S to 16S RNA", Biophysical Society, Boston, Massachusetts, 1965.

Participant at Gordon Conference on Cell Structure and Function, Meriden, New Hampshire, 1965.

"Turn-Over of Mitochondrial DNA" Seminar, National Cancer Institute, Bethesda, Maryland, 1966.

"Isolation and Fractionation of DNA", invited speaker, Symposium on Subcellular Fractionation, London, England, 1967.

"Isolation and Properties of Satellite DNA", University of Edinburgh, Scotland, 1967.

Properties of Mouse Satellite DNA", University of Glasgow, Glasgow, Scotland, 1967.

"Isolation of Complementary Strands from Mouse Satellite", Oxford University, Oxford, England, 1967.

"Highly Repetitive Sequences of DNA", St. Andrews University, St. Andrews, Scotland, 1968.

"Repetitive Sequences in Rodents", Department of Molecular Biology, University of Edinburgh, Edinburgh, Scotland, 1968.

"Satellite DNA from the Guinea Pig", Newcastle University, Newcastle, England, 1968.

"Isolation, Preparation, and Fractionation of DNA", Imperial Cancer Research Fund, London, England, 1968.

"Properties and Possible Role of Satellite DNAs", Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1968.

"Highly Repetitive DNA", Yale University, New Haven, Connecticut, 1968.

"Structure and Function of Repetitive DNA", invited speaker at Conference on Satellite DNA, American Association for the Advancement of Science, Chicago, Illinois, 1968.

"Properties of Guinea Pig DNA", Symposium on Hybridization of Nucleic Acids, Biochemical Society, Newcastle, England, 1968.

"Complementary Strands of Satellite DNAs", Biophysical Society Meeting, Los Angeles, California, 1969.

Participant at Gordon Conference on Cell Structure and Function, Hanover, New Hampshire, 1969.

"Classes of DNA in Mammals", University of North Carolina, Chapel Hill, North Carolina, 1969.

"Structure and Function of Repetitive DNA", Duke University, Durham, North Carolina, 1969.

"Satellite DNAs in Rodent Species", University of Chicago, Chicago, Illinois, 1969.

"Synthesis of DNA Following Alkylation", Temple University, Philadelphia, Pennsylvania, 1970.

"Repetitive DNA", Case Western Reserve University, Cleveland, Ohio, 1970.

"Repetitive Sequences of Higher Organisms", University of Nebraska, Lincoln, Nebraska, 1970

"Alkylation of DNA", Biophysical Society Meeting, Baltimore, Maryland, 1970.

"Structure and Function of Mammalian DNA", University of Texas, Austin, Texas, 1971.

"Repair of Human DNA", National Institute for Environmental Health Sciences, 1971.

"Alkylation and Repair of DNA", Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1971.

"Repetitive Sequences of DNA", Brooklyn College, New York, New York, 1971.

"A Gene Mutational Assay in Mouse Cells", North Carolina State University, Raleigh, North Carolina, 1971.

"Lectures on Chemical Mutagenesis", University of Sao Paulo, Sao Paulo, Brazil, 1971.
"Lectures and Demonstrations on Ultracentrifugation", University of Sao Paulo, Sao Paulo, Brazil, 1971.

"Chemical Mutagens in the Biosphere", Environmental Mutagen Society, Washington, D.C., 1971.

"Molecular Mechanisms of Mutagenesis", invited participant in Workshop on Chemical `Mutagens as Environmental Contaminants, sponsored by the Fogarty International Center, Bethesda, Maryland, 1971.

"Lectures on Chemical and Radiation Biology", Winter Biochemistry Course, sponsored by Organization of American States, 1971.

"Structure and Function of Human Chromosomes", National Science Foundation, Boulder, Colorado, 1971.

Chairman of Workshop on "Somatic Cell Mutagenesis", sponsored by National Institute of Environmental Health Sciences, 1972.

"Repetitive DNA, Chromosome Defects and Neoplasia", sponsored by National Science Foundation, Minneapolis, Minnesota, 1972.

"Mutagenesis in Mammalian Cells", Duke University, Durham, North Carolina, 1972.

"Mutagenicity of Hycanthone", University of Sao Paulo, Sao Paulo, Brazil, 1972.

"Gene Mutations at the Thymidine Kinase Locus", John Hopkins University, Baltimore, Maryland, 1972.

"Repetitive Sequences and Neoplasia", University of Minnesota, Minneapolis, Minnesota, 1972.

"Mutagenicity of Chemical Substances", George Washington University, Washington, D.C., 1973.

"Test Systems for Measuring Mutagenicity", Howard University, Washington, D.C., 1973.

"Lectures on Molecular Biology", University of Zurich, Zurich, Switzerland, 1973.

"Mutagenesis and Repair", Swiss Institute for Experimental Cancer Research, Lucerne, Switzerland, 1973.

"Mutagenic Test Systems", Food and Drug Administration, Washington, D.C., 1973.

"Relationship of DNA Repair to Mutagenesis", invited participant to Workshop on Mutagenic Test Methods, sponsored by National Institutes of Health, Research Triangle

Park, North Carolina, 1973.

"A Tier System Approach to Mutagen Testing", invited speaker at International Conference on Chemical Mutagens, Asilomar, California, 1973.

"*Lectures on Molecular Genetics*", Symposium on Molecular Hybridization, Zurich, Switzerland, 1973.

"A New approach to Mutagen Testing", invited speaker at Symposium on Chemical Mutagenesis, Moscow, USSR, 1974.

"Introduction to Toxicology", Chairman of Symposium on Collaborative Studies in Toxicology, sponsored by Society of Toxicology and the Association of Official Analytical Chemists, Washington, D.C., 1974.

"Relevance of Mutagenicity Tests in Toxicology", Saratoga Conference on Molecular Biology and Pathology, Saratoga Springs, New York, 1974.

"Test Systems for Assessing Mutagenic Potential", invited speaker at Symposium on Collaborative Studies in Toxicology, sponsored by SOT and AOAC, Washington, D.C., 1974.

"Use of Gene Mutational Assays as a Model for Risk Assessment", Symposium on Risk Assessment, sponsored by NIH, Wrightsville Beach, North Carolina, 1974.

"Tier System Approach to Mutagen Testing", National Institute of Health, Research Triangle Park, North Carolina, 1974.

"Carcinogenesis and Mutagenesis", Procter and Gamble Co., Cincinnati, Ohio, 1975.

"The Need to Quantify Risk", National Cancer Advisory Board, Bethesda, Maryland, 1975.

"Mechanisms of Mutagenesis", General Foods Corporation, New York, New York, 1975.

"Problems in Carcinogenesis", Worcester Foundation for Experimental Biology, Worcester, Massachusetts, 1975.

Chairman of Workshop for Developing a Document on "Mutagenic Test Procedures", Ocean City, Maryland, 1975.

"Mutagenesis as a Toxicologic Problem", Chairman of Gordon Conference Session on

Mutagenesis, Meriden, New Hampshire, 1975.

"Open Meeting on Mutagenesis", sponsored by National Institutes of Health, Bethesda, Maryland, 1975.

"Mutagenic Test Systems", Chairman of Session on Short-Term Test, Symposium entitled, "Toxicology and the Food Industry," Aspen, Colorado, 1975.

Session Chairman, Symposium on In Vitro Mutagenicity Tests, Environmental Mutagen Society, Miami, Florida, 1975.

Workshop on "Principals for Evaluating Chemicals in the Environment", sponsored by the National Academy of Sciences, San Antonio, Texas, 1975.

Open Meeting on Mutagenesis, sponsored by DHEW, Bethesda, Maryland, 1976.

"Carcinogenicity Assays, Problems, and Progress", Gordon Conference on Toxicology and Safety Evaluation, Meriden, New Hampshire, 1976.

"Value of Short-Term Tests in Carcinogenesis", Toxicology Forum, Aspen, Colorado, 1976.

"Presumptive Tests", Symposium on Risk Assessment entitled, "Extrapolation II", sponsored by DHEW, Pinehurst, North Carolina, 1976.

"Programs of the National Cancer Institute", invited speaker on cancer, sponsored by the American Association of Science, Boston, Massachusetts, 1976.

"Assessment of Risks from Carcinogenic Hazard", invited speaker to Symposium on Toxicology, sponsored by Synthetic Organic Chemists Manufacturing Association, Atlanta, Georgia, 1976.

Chairman of Session on Short-Term Tests, Symposium on "Status of Predictive Tools in Application to Safety Evaluation", Little Rock, Arkansas, 1976.

"Relevance of Carcinogenicity Testing to Humans", invited speaker at Origins of Human Cancer Cold Spring Harbor Symposium, 1976.

"Human Genetic Disease Versus Mutagenicity Assays", Symposium sponsored by Pharmaceutical Manufacturers Association, Sea Island, Georgia, 1976.

Open Meeting on Mutagenesis, sponsored by DHEW, Bethesda, Maryland, 1976

"Role of the NCI in the National Cancer Program on Environmental Carcinogenesis", invited speaker at Conference on Aquatic Pollutants and Biological Effects with Emphasis on Neoplasia, New York Academy of Sciences, New York, New York, 1976.

"Genetic Disease in Human and Mutagenic Test Systems", Albany Medical School, Albany, New York, 1976.

"Statistical Problems in Carcinogenesis", University of California, Berkeley, California, 1976.

"Carcinogenesis and Animal Bioassay", Grocery Manufacturers of America, Washington, D.C., 1976.

"Problems and Needs in Assessing Carcinogenicity Data", National Clearinghouse for Environmental Carcinogens, 1976.

"Carcinogenesis and Cancer Prevention", University of Eastern Virginia Medical College, Norfolk, Virginia, 1977.

"Overview of Mutagenesis", Food and Drug Administration, Washington, D.C., 1977.

Workshop on Carcinogenicity of Aromatic Amines and Hair Dyes, International Agency for Research in Cancer, Lyon, France, 1977.

"Strengths and Weaknesses of Current Approaches in Carcinogenesis", session Chairman and speaker on "Federal Regulation of Environmental Carcinogens," Center for Continuing Education, Washington, D.C. 1977.

"Program in Carcinogenesis", Cancer Research Safety, NIH, Dulles Airport, Virginia, 1977.

"Predictive Value of Short-Term Tests", invited speaker at Animal Health Institute, Lake Tahoe, Nevada, 1977.

Open Meeting on Mutagenesis, sponsored by DHEW, Bethesda, Maryland, 1977.

"Risk Evaluation", in the Federal Regulation of Environmental Carcinogens, sponsored by Center for Continuing Education, Washington, D.C., 1977.
"Statistical Considerations of the Dominant Lethal and Heritable Translocation Test", The Washington Statistical Society, 1978.

"Testing: Short-Term", 3rd Toxic Substances Control Conference, Government Institutes, Inc., Washington, D.C., 1978.

"The Degree of Concern as Defined by Short-Term Carcinogenicity Assays", Pharmaceutical Manufacturers Association, Point Clear, Alabama, 1978.

"Short-Term Predictive Tests", Pharmaceutical Manufacturers Association, Lincolnshire, Illinois, 1978.

Chairman of Scientific Review Meeting on the U.S. Environmental Protection Agency Diesel Emission Health Effects Research Program, U.S., EPA, Washington, D.C., 1978.

"Strengths and Weaknesses of Tests for Mutagenesis", Banbury Center of the Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, 1978.

"Detecting and Measuring Carcinogens", Seminar on Government Regulation of Cancer Causing Chemicals, National Center for Administrative Justice, Washington, D.C., 1978.

Workshop on "Chemical Scoring Systems", Interagency Testing Committee (TSCA), San Antonio, Texas, 1978.

"Needs for Regulatory Utility of Short-Term Test Data", International Update on Short-Term Tests, The Toxicology Forum, Washington, D.C., 1979.

"Proposed Application of Short-Term Tests", International Update on Short-Term Tests, The Toxicology Forum, Washington, D.C., 1979.

"Current and Proposed Use of Short-Term Tests", Cosmetic, Toiletry and Fragrance Association, Washington, D.C., 1979.

"Application of Mutagenicity Testing on SOM Food Animal Drugs", Subcommittee on Environmental Mutagenesis, DHEW/CCTRP, 1979.

"Application of Mutagenicity Testing in Cyclic Review of Food Additives", Subcommittee on Environmental Mutagenesis, DHEW/CCTRP, 1979.

"Recent Developments on Sorbate/Nitrite", Tripartite (U.S., Canada, U.K.), Annapolis, Maryland, 1979.

"What is Risk?", International Course on the Detection of Environmental Mutagens, Concepcion, Chile, 1979.

"Status of Regulations and Proposed Regulation Covering Environmental Mutagens", International Course on the Detection of Environmental Mutagens, Concepcion, Chile, 1979.

"Food Safety Guidelines", Tripartite (U.S., Canada, U.K.), Ottawa, Canada, 1980.

"History and Progress in Carcinogenesis", Society of Cosmetic Chemists, 1978.

"Introduction and History of Mutagenicity Testing", Annual Meeting of the American College of Toxicology, 1980.

Mutagenicity and Neoplastic Transformation Assays, Course on "Identification and Quantification of Environmental and Occupational Carcinogenic Risks", sponsored by the American College of Toxicology, 1980.

Lectured on Molecular Mechanisms at the American College of Toxicology's course on "Identification of Environmental and Occupational Carcinogenic Risks." "Introduction and History of Environmental Mutagenesis", Second Annual Meeting of the American College of Toxicology.

"Risk-Benefit Considerations in Toxicology", The Toxicology Forum, 1981 Winter Meeting.

"Trends in Biosassay Methodology", 75th Anniversary of the Food and Drug Act, Sponsored by the Animal Health Institute.

"Relationship Between Science & Regulation", Food and Drug Administration Risk Assessment for Carcinogenic Food Ingredients - EPA, 1982.

FDA Experience with Risk Assessment for Carcinogens in Foods, Food and Drug Law Institute, 1982.

Practical Applications of Risk Analysis, The Food, Drug and Law Institute Conference, 1982.

The Future of Carcinogen Testing: Implications for Food Safety, A Symposium on Food Safety Laws: Delaney and Other Dilemmas, sponsored by Boston University, 1982.

Regulatory Use of Genetic Toxicity, Tests, Society of Toxicology - Mid Atlantic Chapter Meeting on Genetic Toxicology/Predictive or Not, 1983.

Aerosol Spray Adhesives, A Workshop on Principles and Applications of Cytogenetic, Sister Chromatid Exchange, Gene Damage to Problems of Human Health, sponsored by the American College of Toxicology, 1982.

Food and Drug Adminstration Viewpoint on Problem Tumor, Toxicology Forum, Winter Meeting, 1983.

Food-Borne Carcinogens, Second International Conference on Safety Evaluations and Regulations of Chemicals, sponsored by Boston University, 1983.

Carcinogenicity of Hair Dyes, Formaldehyde, Nitrates and Berylliu, Symposium on Interpretation of Epidemiological Evidence, sponsored by International Agency for Research on Cancer, 1983.

Use of Acute Toxicity Studies in the Bureau of Foods, Acute Toxicity Workshop, sponsored by the Food and Drug Administration, 1983.

Critical Issues on Science, Technology and Future, The Brookings Institution, 1983.

Challenge to Animal Testing, Chemical Manufacturers Association, 1983.

Regulatory Significance of Workshop Recommendation on Alternatives to Animal Testing, Workshop on Acute Toxicity Testing - Alternative Approaches, sponsored by Johns Hopkins University, 1983.

Role of Mathematical Models in Assessment of Risk and in Attempts to Define Management Strategy, Safety Assessment: The Interface Between Law and Regulation, sponsored by International Life Science Institute, 1983.

Impact of Short-Term Tests on Regulatory Actions, Conference on Cellular Systems for Toxicity Testing, sponsored by New York Academy of Sciences, 1984.

Requirements of Pre-Market Evaluation, Toxicology Forum, April Meeting, 1984.

Use of Short-Term Tests in Risk Assessment, Workshop on RA/RM: Carcinogenesis, sponsored by Society for Risk Analysis, 1986.

A Regulator's Viewpoint, Workshop on Risk Assessment, sponsored by The Procter and Gamble Co., 1986.

Risk Assessment, Sensitivity Analysis, GMA Technical Committee Food Protection Meeting, Grocery Manufacturers of America, 1986.

Update on Current Approaches in Addressing Threshold of Regulations and DeMinimus Risk, Toxicology Forum, Winter Meeting, 1986.

Toxicity Update on BHA/BHT, Toxicology Forum, Aspen Meeting, 1985.

Food Regulatory Issues, Washington Chemical Society, 1984.

Issues in Decision Making, Interdisciplinary Discussion Group in Carcinogenicity Studies, sponsored by ILSI, 1986.

Recent Developments in Risk Assessment, Medical Issues in Toxic Tort Cases: Risk Assessment, Cancer, and Immunological Injuries, sponsored by the American Bar Association, 1987.

Replacement of the LD_{50} Tests at the Food and Drug Administration, Workshop on Alternative Tests, sponsored by Mobil Oil, 1987.

Risk Assessment/Oncology and Regulatory Issues, The American College of Toxicology, Annual Meeting, 1987.

The Need for Situational Analysis and Scientific Judgment in Assessing the Risk from Chemical Carcinogens, New York Academy of Sciences, 1987.

Summary of "Workshop on the Role of Liver Enzyme Induction in Carcinogenesis and Drug Interaction", sponsored by Merk, Sharp and Dohme Laboratories, 1988.

Issues and Directions for the Future, Society for Risk Analysis, Annual Meeting, 1988.

Pros and Cons of Quantitative Risk Analysis, Institute for Food Technology, Basic Symposium, 1988.

Threshold of Regulation for Indirect Food Additives, Workshop on DeMinimus Risk, 1985.

Possible Mechanisms of BHA Carcinogenicity in the Rat, Food Antioxidants: International Perspectives, sponsored by ILSI, 1986.

In Vitro Toxicology, General Principles and Concepts in Toxicology and Toxicologic Pathology, Course sponsored by University of Cincinnati, 1987.

Risk Assessment in Product Regulation, Prevention 85, sponsored by the American College of Preventive Medicine, 1985.

Establishment of Acceptable Limits of Intake, Second National Conference for Food Protection, 1984.

Use of Short-Term Test Data in Cancer Risk Assessment, Society of Toxicology Annual Meeting (Course), 1988.

Critical Assessment of Carcinogen Risk Policy, International Society of Regulatory

Toxicology and Pharmacology, 1988.

The Food and Drug Administration Procedures and Policies to Estimate Risks of Injury to the Male Reproductive System, Sperm Measures and Reproductive Success, sponsored by Georgetown University, 1988.

Risk Assessment of Food and Color Additives, United States-Japan Workshop on Risk Assessment/Risk Management sponsored by The Environmental Protection Agency and Osaka University, 1988.

How Molecular Data is Used in Risk Assessment, Banbury Conference on New Directions in the Quantitative and Qualitative Aspects of Carcinogen Risk Assessment, 1988.

How has the Delaney Clause Impacted on The Food and Drug Administration and Public Health, Food and Drug Law Institute Symposium on The Delaney Clause, 1988.

Presentations at the Toxicology Forum 1989-1994.

American College of Toxicology – Annual Meeting – "Does the Term Carcinogen Send the Wrong Message", Dec. 1998.

PUBLICATIONS:

Shirkey, H.C., Schmidt, G.C., Miller, R.G., and Flamm W.G., "Animal Sera and Specific Enzymes in the Treatment of Poisoning", Journal of Pesticides, 60:711, 1962.

Flamm, W.G., and Crandall, D.I., "Evidence for the Existence of Ferrous Mercaptans in the Active Center of Homogentisate Oxidase", Federation Proc., 21:250, 1962.

Flamm, W.G., and Crandall, D.I., "Purification of Mammalian Homogentisate Oxidase and Evidence for the Existence of Ferrous Mercaptans in the Active Center", J. Biol. Chem., 238:389, 1963.

Flamm, W.G., "Purification of Homogentisate Oxidase and an Investigation of its Properties and Active Center", Dissertation Abstracts, 23:1503, 1962.

Flamm, W.G., Birnstiel, M.L., and Filner, P., "Protein Synthesis in Isolated Nuclei of Exponentially Dividing Cells", Biochem. Biophys. Acta., 76:110, 1963.

Flamm, W.G., and Birnstiel, M.L., "Studies on the Metabolism of Nuclear Basic Proteins in Nucleohistones," In: Bonner, J., and Ts'o, P. (Ed.): The Nucleohistones, San Francisco,

Holden-Day, Inc., 1964, pp. 230-41.

Flamm, W.G., and Birnstiel, M.L., "Nuclear Synthesis of Ribosomes in Cell Cultures", Biochem. Biophys Acta., 87:101, 1964.

Flamm, W.G., and Birnstiel, M.L., "Inhibition of DNA Replication and its Effect on Histone Synthesis", Experimental Cell Research, 33:616, 1964.

Birnstiel, M.L., Chipchase, M.I.H., Flamm, W.G., "The Chemical Composition and Organization of Nucleolar Proteins", Biochem. Biophys. Acta., 87:111, 1964.

Nicholson, M., and Flamm, W.G., "The Fate of Functional Ribosomes in Tobacco Cell Cultures", Federation Proc., 23:316, 1964.

Birnstiel, M.L., and Flamm, W.G., "On the Intranuclear Site of Histone Synthesis", Science, 145:1435, 1964.

Flamm, W.G., and Nicholson, M., "Synthesis of RNA in Cultured Tobacco cells", Biology, Pasadena, California Institute of Technology, 1964, pp. 136-41.

Nicholson, M., and Flamm, W.G., "Properties and Significance of Free and Bound Ribosomes from Cultured Tobacco Cells", Biochem. Biophys. Acta., 108:266, 1965.

Flamm, W.G., Counts, W.B., and Banerjee, M.R., "Inhibition of RNA Synthesis in Mouse Skin by actinomycin D and 7,12-dimethylbenz(a)anthracene", Nature, 210:541, 1966.

Flamm, W.G., Banerjee, M.R., and Counts, W.B., "Topical Application of Actinomycin D on Mouse Skin: Effect on the Synthesis of RNA and Protein", Cancer Research, 26:1349, 1966.

Counts, W.B., and Flamm, W.G., "An Artifact Associated with the Incorporation of Thymine into DNA Preparations", Biochem. Biophys. Acta., 114:628, 1966.

Flamm, W.G., Counts, W.B., and Bond, E., "Conversion of 23S to 16S RNA: Evidence of Heterogeneity within the 23S Fraction", Abstracts Biophysical Society, 10:7, 1966.

Banerjee, M.R., Flamm, W.G., and Counts, W.B., "Effect of Actinomycin D on RNA and Protein Synthesis in Mouse Skin", Proc. of the Amer. Assn. for Cancer Research, 7:5, 1966.

Bond, E., Flamm, W.G., and Burr, H.E., "Intracellular Location and Metabolism of Satellite DNA in Mouse Liver", American Zoologist, 6:308, 1966.

Flamm, W.G., Bond, E., and Burr, H.E., "Density Gradient Centrifugation of DNA in a Fixed-

Angle Rotor· A Higher Order of Resolution", Biochem. Biophys. Acta., 129:310, 1966.

Flamm, W.G., Bond, E., Burr, H.E., and Bond S., "Satellite DNA Isolated from Mouse Liver: Some Physical and Metabolic Properties", Biochem. Biophys. Acta., 123:652, 1966.

Bond, E., Flamm, W.G., Burr, H.E., and Bond, S., "Mouse Satellite DNA: Further Studies on its Biological and Physical Characteristics and its Intracellular Localization", J. Mol. Biol., 27:289, 1967.

Flamm, W.G., McCallum, M., and Walker, P.M.B., "The Isolation of Complementary Strands from a Mouse DNA Fraction", Proc. Natl. Acad. Sci., 57:1729, 1967.

Flamm, W.G., McCallum, M., and Walker, P.M.B., "Isolation of Complementary Strands from Mouse Satellite DNA", Biochemical J., 104:38-9, 1967.

Flamm, W.G., "Use of Fixed-Angle Rotors for the Banding of DNA in CsCl Density Gradients", Measuring & Scientific Equipment Ltd., Newsletters (London):A2, 1967.

Flamm, W.G., Birnstiel, M.L., and Walker, P.M.B., "Preparation, Fractionation and Isolation of Single Strands of DNA by Isopycnic Ultracentrifugation in Fixed-Angle Rotors", In: Birnie, G.D. (Ed.), Subcellular Components. London, England, Butterworth Publishing Co., 1968, p. 125.

Walker, P.M B., Flamm, W.G., and McLaren, A. "The Problem of Highly Repetitive DNA in Higher Organisms", In: Lima-De-Faria, A. (Ed.), Handbook of Molecular Cytology. Amsterdam, North Holland Publishing Co., 1969.

Flamm, W.G., McCallum, M., and Walker, P.M.B., "Guinea Pig Satellite DNA: Renaturation Characteristics and Strand Separation", Biochemical J., 108:42, 1968.

Flamm, W.G., Walker, P.M.B., and McCallum, M., "Some Properties of the Single Strands Isolated from the DNA of the Nuclear Satellite of the Mouse (mus musculus)", J. Mol. Biol., 40:423, 1969.

Flamm, W.G., McCallum, M., and Walker, P.M.B., "On the Properties and the Isolation of Individual Complementary Strands of the Nuclear Satellite of Guinea Pig DNA", J. Mol. Biol., 42:441, 1969.

Adam, K.M.G., Blewett, D.A., and Flamm, W.G., "The DNA of Acanthamoeba: A Method for Extraction and Its Characterization", J. Protoz, 16:6, 1969.

Flamm, W.G., Walker, P.M.B., and McCallum, M., "Satellites from Nuclear DNA: Large Variation in Properties Among the Genera of Rodentin", Biophysical Journal, 13:219, 1969.

Fishbein, L., Flamm, W.G., and Falk, H.L., Chemical Mutagens in Man's Environment. New York, Academic Press, 1970, p. 360.

Flamm, W.G., Bernheim, N.J., and Spalding, J., "Selective Inhibition of the Semiconservative Replication of Mouse Satellite DNA", Biochem. Biophys. Acta., 195:273, 1969.

Brubaker, P.E., Flamm, W.G., and Bernheim, N.J., "Effect of Y Chlordane on Synchronized Lymphoma Cells: Inhibition of Cell Division", Nature 226:548, 1970.

Flamm, W.G., Bernheim, N.J., and Fishbein, L., "On the Existence of Intrastrand Crosslinks in DNA Alkylated with Sulfur Mustard", Biochem. Biophys. Acta., 223:657, 1970.

Flamm, W.G., Bernheim, N.J., and Brubaker, P.E., "Density Gradient Analysis of Newly Replicated DNA from Synchronized Mouse Lymphoma Cells", Experimental Cell Research, 64:97, 1971.

Flamm, W.G., Birnstiel, M.L., and Walker, P.M.B., "Isopycnic Centrifugation of DNA: Methods and Applications", In: Birnie, G.D. (Ed.), Subcellular Components. London, England, Butterworth Publishing Co., 1968, pp. 279-310.

Flamm, W.G., "Chemical Mutagenesis", In Chemical and the Future of Man, Hearings before the Subcommittee on Executive Reorganization and Government Research. U.S. Senate. U.S. Government Printing Office, April, 1971, pp. 27-31.

Flamm, W.G., "Highly Repetitive Sequences of DNA in Chromosomes", International Review of Cytology, 32:1-55,1972.

Clive, D., Flamm, W.G., and Machesko, M., "Mutagenicity of Hycanthone in Mammaliam Cells", Mutation Research, 14:262, 1972.

Flamm, W.G., and Drake, J., "The Molecular Basis of Mutation", In: Sutton, H.E., and Harris, M., (Ed.), Mutagenic Effects of Environmental Contaminants. New York, Academic Press, 1972, pp. 15-26.

Clive D., Flamm, W.G., Macesko, M.R., and Bernheim, N.J., "A Mutational Assay System Using the Thymidine Kinase Locus in Mouse Lymphoma Cells", Mutation Research, 16:77-87, 1972.

Clive, D., Flamm, W.G., Machesko, M.R., and Bernheim, N.J., "An In Vitro System for Quantitating Mutations at the Thymidine Kinase Locus in L5178Y Mouse Lymphoma Cells", Mutation Research, 21:7-8, 1973.

Clive, D., Flamm, W.G., and Patterson, J., "Specific Locus Mutational Assay Systems for Mouse Lymphoma Cells", In: Hollaender, A. (Ed.) Chemical Mutagens, Volume III. New York, Plenum Press, 1973, 790.

Fishbein, L., and Flamm, W.G., "Potential Environmental Chemical Hazards, Part I. Drugs", *The Science of the Total Environment*, 1:15-30, 1972.

Fishbein, L., and Flamm, W.G., "Potential Environmental Chemical Hazards, Part II. Feed Additives and Pesticides", The Science of the Total Environment, 1:31-64, 1972.

Fishbein, L., and Flamm, W.G., "Potential Environmental Chemical Hazards, Part III. Industrial and Misellaneous Agents", The Science of the Total Environment, 1:117-140, 1972.

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Flamm, W.G., "A Tier System Approach to Mutagen Testing", Mutation Research, 26,329-333, 1974.

Flamm, W.G., "Test System for Assessing Mutagenic Potential", J. Amer. Assn. of Analytical Chemists, 58:668-671, 1975.

Flamm, W.G., "Introduction: Need for Collaborative Studies", J. Amer. Assn. of Analytical Chemists, 58, 1975.

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Flamm, W.G., Guest Editorial, "The Need for Quantifying Risk from Exposure to Chemical Carcinogens", Preventive Medicine, 5:4-6, 1976.

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Green, S., Moreland, F.M., and Flamm, W.G., "A New Approach to Dominant Lethal Testing", Toxicology and Applied Pharmacology, 39:549-552, 1977.

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Flamm, W.G., "Risk Assessment Policy in the United States", Risk and Reason: Risk Assessment in Relation to Environmental Mutagen and Carcinogens, Alan R. Liss, Inc., 141-149, 1986.

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Flamm, W.G., "Pros and Cons of Risk Assessment "In J. Taylor and R. Scanlan (Eds.) Food Toxicology: A Perspective on the Relative Risks," Marcel Dekker Publ. pg. 429-446, 1989.

Scheuplein, R.J., and Flamm, W.G., "An Historical Perspective on FDA's Use of Risk Assessment." In: Philip Shubik and Roger Middlekauf (Eds). International Food Regulation Handbook, Marcel Dekker, Inc. pg. 27-51, 1989.

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Flamm, W.G., and Lehman-McKeeman, "The Human Relevance of the Renal Tumor-Inducing Potential of d-Limonene in Male Rats: Implications for Risk Assessment" Reg. Tox. and Pharmacol. 13,70-86, 1991.

Gori, G., and Flamm, W.G., "How Sick A Patient? Report on Workshop on Cancer Risk Assessment" Regulatory Tox. and Pharmacol. 14, 1-8, 1991.

Ashby, J., Doerrer, N.G., Flamm, W.G., et al. "A Scheme for Classifying Carcinogens" Regulatory Tox. and Pharmacol. 12, 270-295, 1990.

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Flamm, W.G., and Hughes, D.H., "Does the Term Carcinogen Send the Wrong Message?", Cancer Letters, 117, 189-194, 1997.

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Burdock, G.A., and Flamm, W.G. "A Review of the Studies of the Safety of Polydextrose in Food" Food and Chemical Toxicol. 37, 233-264, 1999.

Carabin I.G., and Flamm, W.G. (1999) Evaluation of the Safety of Inulin and Oligofructose as Dietary Fiber, Regulatory Tox. and Pharm. 30, 268-282.

Burdock G.A., Flamm, W.G. and Carabin, I.G. (2000) Toxicity and Mutagenicity Studies of DN-50000 and RP-1 Enzyme, Food and Chem. Tox. 38, 429-442.

Flamm, W.G. (2001) Elevating the Terms of the GM Food Debate, Regulatory Tox. and Pharm. 33, 1

Soni, M.G., White, S., Flamm, W.G. and Burdock, G.A. Safety Evaluation of Dietary Aluminum, Regulatory Tox. and Pharm., 33, 66-79, 2002.

Burdock, G.A. and Flamm, W. G. Review Article: Safety Assessment of the Mycotoxin Cyclopiazonic Acid, International Journal of Toxicology 19:195-218, 2000.

Flamm, G., Glinsmann, W.H., Kritchevsky, D. Prosky, L. and Roberfroid, M. Inulin and Oligofructose as Dietary Fiber: A Review of the Evidence, Critical Reviews in Food Science and Nutrition, 41, 353-362, 2001.

CURRICULUM VITAE

DOUGLAS L. ARCHER, PH.D.
PROFESSOR AND PAST CHAIR

Assistant Surgeon General (ret)

I. **PERSONAL DATA**

Home Address:

Business Address: Food Science & Human Nutrition Department
University of Florida
359 FSHN Building, Newell Drive
PO Box 110370
Gainesville, FL 32611-0370

Telephone:

Facsimile:

E-Mail:

II. **EDUCATION**

B.A. - Zoology (1968)
University of Maine, Orono, ME

M.S. - Bacteriology (1970)
University of Maine, Orono, ME

Ph.D. - Microbiology (1973)
University of Maryland, College Park, MD

III. **SERVICE** 12/73 to 12/93: Commissioned Officer, U. S. Public Health Service - Retired
1/1/94: **Assistant Surgeon General** (Rear Admiral)

IV. EXPERIENCE

January 2, 2001 - Present:
Professor of Food Science and Human Nutrition, University of Florida.

January 3, 1994 - January 1, 2001:
Professor and Chair, Food Science and Human Nutrition Department, University of Florida, Institute of Food and Agricultural Sciences

November 6, 1992 - December 31, 1993:
Deputy Director for Programs, Center for Food Safety and Applied Nutrition, FDA.

December, 1989 - November 6, 1992
Deputy Director, Center for Food Safety and Applied Nutrition, FDA.

February, 1991 - July, 1991
Acting Director, Office of Seafood, Center for Food Safety and Applied Nutrition, FDA

February, 1986 - December, 1989:
Director, Division of Microbiology, Center for Food Safety and Applied Nutrition, FDA

1983 - 1986: Deputy Director, Division of Microbiology, Center for Food Safety and Applied Nutrition, FDA.

1975 - 1983: Research Team Leader, Immunobiology, Division of Microbiology, FDA, Cincinnati, Ohio.

1979 - 1983: Adjunct Assistant Professor of Toxicology, University of Cincinnati College of Medicine.

1973 - 1975: Research Microbiologist, Division of Microbiology, Bureau of Foods, Washington, DC.

1970 - 1973: Graduate Teaching Assistant, Department of Microbiology, University of Maryland, College Park, Maryland.

1968 - 1970: Graduate Teaching Assistant, Department of Microbiology, University of Maine, Orono, Maine.

V. **AWARDS**

2000: **Advancement of Industry Award**-American Meat Institute. "For outstanding service to the industry and consumers by defending sodium nitrite safety."

1993: **Distinguished Service Medal** for "Exceptional and Distinguished Career" in support of public health in the U.S.

1993: **U.S. Public Health Service Meritorious Service Medal** for "an extraordinary degree of commitment and dedication to food safety research, and to the development and implementation of public health and education programs."

1992: **J.C. Frazier Memorial Award**, Food Research Institute, "In recognition of outstanding achievements in the field of food Microbiology." Madison, WI.

1992: **U.S. Public Health Service Outstanding Unit Citation** for exemplary performance of duty - For leadership demonstrated during the implementation of the Nutrition Labeling and Education Act of 1990.

1991: **Appointed Assistant Surgeon General, USPHS.**

1989: **U.S. Public Health Service Citation** for outstanding leadership of the microbiological programs of CFSAN.

1989: **U.S. Public Health Service Meritorious Service Medal** for sustained superior performance in the management and scientific leadership of FDA's research and regulatory efforts in the area of food safety.

1988: **Tanner Memorial Award** - Institute of Food Technologists - Outstanding Individual in Food Technology and Related Sciences. Award Lecture: "The True Health Impact of Foodborne Disease".

1987: **Commissioner's Special Citation** for "In recognition of sustained superior management performance and national and international recognition as an expert in the area of food safety and microbiology.

1986, 87, 88, 89: **U.S. Public Health Service Citation** for Outstanding Performance.

1984: **U.S. Public Health Service Meritorious Service Medal** for sustained high-quality leadership and professional accomplishments in microbiological toxicology research and providing research direction for the Division of Microbiology, ONFS.

1979: **U.S. Public Health Service Commendation Medal** for development of in vitro immunological systems.

VI. THESIS

M.S. Degree: A comparison of swarming and motility in Proteus mirabilis and a variant.

Ph.D. Degree: Control of interferon, virus capsid antigens, and migration inhibitory factor in Burkitt's Lymphoma-derived cell lines:Role of L-arginine.

VII. ORGANIZATIONS

Member, Board of Directors, Life Sciences Research Office (LSRO), 1999 - 2003.

Commissioned Officers Association, USPHS, 1973 - Present.

Food Allergy Network, February 1994 - Present.

Institute of Food Technologists (IFT), elected professional member, 1989 - Present.

IFT - Contributing Editor, Food Technology, 2001 - Present.

IFT Florida Section, 1994 - Present.

IFT Committee on Education, September 1, 1994 - August 31, 1997; Appointed Secretary, March 1996 - 1998.

IFT Toxicology and Safety Evaluation Division, Appointed to the Executive Committee, August 1995 - August 1998.

IFT Florida Section, Elected Councilor, September 1995 - August 1997.

IFT Task Force Steering Committee on Food Safety Initiatives, October 1997 - Present.

IFT Science, Communications and Government Relations Committee, Member.

IFT Task Force on Sound Science, 2002 - Present

IFT Committee on Codex Alimentarius, 2002 - Present

VIII. PROFESSIONAL ACTIVITIES

International

U.S. Representative, WHO Expert Advisory Panel on Food Safety, January 1990 - February 2006.

Chairman, Codex Alimentarius Food Hygiene Committee, FAO/WHO, 1985 - 1994.

Chairman, ILSI Europe/WHO Workshop on a Scientific Basis for Regulations on Pathogenic Microorganisms in Foods. May 17-19, 1993, Brussels, Belgium.

F.D.A. negotiator with European Community, 1990, Washington, DC; Head of Foods Delegation 1991, Brussels, Belgium.

U.S. Representative to the Tripartite Microbiology Subcommittee, London, England, November 1985 - 1993.

Member and U.S. Delegation Chairman, 1986 -1990. U.S. (AOAC) Representative to International Dairy Federation meeting and Chairman, dilutions methodology, Helsinki, Finland, 1984.

U.S. (AOAC) Delegate to International Standards Organization, Helsinki, Finland, 1984.

Consultant to WHO Committee on Listeria in Foods, 1988.

Advisor to Australian Government on formation of the Australian National Food Authority, April, 1991.

International Meat and Poultry HACCP Alliance, Scientific Advisory Committee Member, 1994 - Present.

Consultant to United Fresh Fruit and Vegetable Association, Produce Microbiology Committee; Allied Trade Associations, International Trade Council; 1994 - 1998.

Editorial Boards

Editorial Board Member, Food Control, 1989 - Present.
Contributing Editor, Food Technology, IFT, 2001-Present

Food Allergy Network, February 1994 - Present.

Member, Board of Publications of Fundamental and Applied Toxicology, Society of Toxicology, May 1983 - 1986.

Advisory Board Member, Academic Press Nutrition and Food Science Publications, 1987 - Present.

Editorial Board Member, Journal of Natural Toxins, 1991 - 1995.

North American Editor, Food Control, Elsevier, Ltd. October 1994 - 1999.

Domestic & Government-Related

Consultant, Centers for Disease Control, Review of Draft Plan for the Detection, Prevention, and Control of New, Reemerging, and Drug Resistant Infectious Diseases, March 22-23, 1993.

Member, Advisory Committee to the Center for Veterinary Medicine, Safety of Sometribove (bovine somatotropin), March 31, 1993.

Public Service Fellow, Woodrow Wilson National Foundation Fellowship, 1993 academic year - Rocky Mountain College, Billings, MT.

Public Health Service Overall Coordinator, L-Tryptophan/Eosinophilia-Myalgia Syndrome Crisis, October, 1989 - 1994.

Member, Government Steering Committee to Institute of Food Technology Research Committee, 1987 - 1994.

Voting Member, National Advisory Committee on Microbiological Criteria for Foods 1989 - November 1994.

Chairman, NACMCF Subcommittee on Risk Assessment, January 1993 - November 1994.

Food Update Board of Governors, Food and Drug Law Institute Food Update, 1991 - 1993.

Consultant, Centers for Disease Control, writing of the "Recommendations for Preventing Transmission of Infection with HTLV-III/LAV in the Workplace, November 1985.

Commissioner's Advisory Group on Women's Health Issues: Infectious Diseases, 1987 - 1988.

Member, External Avisory Board, Center for Food Safety, Institute of Food Science and Engineering, Texas A & M University System, October 1995 - 1998.

Member, Cyclospora Advisory Panel, California Strawberry Commission, June 1996

Consultant to the FDA Food Advisory Committee on the Safety of Calgene Tomatoes, Washington, DC, April 7-9, 1994.

University of Florida (UF),
Institute of Food and Agricultural Sciences (IFAS),
and Academic Related Activities

Co-Chair, On-Campus Re-structuring Task Force, 2002.

IFAS representative to Florida Food Safety Council, 2002.

IFAS representative to UF Bioterrorism Task Force, 2001-Present

Appointed to the UF University Senate, Member, 1994-96.

UF World Food Day Committee, Member, 1994.

Member - UF, College of Veterinary Medicine, Center for Environmental and Human Toxicology (CEHT) Search Committee for the position of Director, CEHT, Member, October 1994.

Member - IFAS Chairs' Subcommittee to Review the Task Force 1995 Recommendations for the Annual Faculty Achievement, Planning, and Evaluation Requirements and Forms, May 1995.

Chair - Program Committee and Steering Committee for the October 28-30, 1996, UF/IFAS Statewide Faculty Meeting, March 8, 1996.

Chair - Committee for the Aquatic Food Products Laboratory Building Dedication, August 1996 - April 1997.

Member - Search and Screen Committee for the UF Associate Director of Development and Alumni Affairs Position, August 1996.

Discussion Leader at the Institute for Academic Leadership, Department Chairs Workshop, Howey-in-the-Hills, FL, October 6-9, 1996.

Facilitator - UF's Workshop on Academic Management, Maximizing Your Leadership Potential, "Dealing with Institutional Conflict/Small Group Discussion", Camp Weed, FL, May 19, 1997.

Industry Repreentative - West Palm Beach Town Meeting, regarding Florida's needs of minimizing microbiological food safety risks for produce, West Palm Beach, FL, December 5, 1997.

Teaching Related

Guest Lecturer in FOS 3042, Introduction to Food Science, "Food Safety Laws and Regulations," April 15 and 18, 1994.

Guest Lecturer in FOS 6915, Research Planning, "An Overview of Graduate Student Responsibilities and Expectations," September 6, 1994; August 29, 1995.

Team teach in Fall, Spring, and Summer terms, FOS 2001, Man's Food, 3 Credit Course, January 1995 - 2000.

Guest Lecturer in FOS 4731, Government Regulations and the Food Industry.

Guest Lecturer in AGG 4932/5932, Hazard Analysis Critical Control Point (HACCP) Systems, "Microbial Concerns in the Food Industry"

Student Related

Past Committees:

000076

1995	Member
1996	Member
1997	Member
1997	Member

1998	Member
1998	Member
1999	Member
2000	Co-chair
2000	Member
2000	Member
2001	Co-chair
2002	Member

	Member
	Member
	Member
	Member
	Member
	Co-Chair
	Member
	Member

IX. PAPERS PRESENTED

Over 160 presentations made to 2001. List available on request.

X. BIBLIOGRAPHY

A. BOOKS

Marshall, Maurice and Archer, Douglas. Your Food and Health: A Study Guide for Man's Food. Second Edition. Kendall/Hunt Publishing Company, Dubuque, IA, 348 pages, 1994; Third Edition, 350 pages, 1995; Fourth Edition, 352 pages, 1996.

B. PUBLICATIONS

1. Archer, D. L. and Young, B. G. Control of interferon, migration inhibitory factory, and virus capsid antigens in Burkitt's Lymphoma-derived cell lines: Role of L-arginine. Infect. & Immun. 9:684, 1974.

2. Archer, D. L., Bukovic-Wess, J. A., and Smith, B. G. Gallic acid: A potential chemical tool for studying cellular interactions involved in the in vitro immune response. IRCS Med. Sci. 4:553, 1976.

3. Archer, D. L., Bukovic-Wess, J. A., and Smith, B.G. Inhibitory effect of an antioxidant, butylated hydroxyanisole, on the primary in vitro immune response. Proc. Soc. Exp. Biol. Med. 154:289, 1977.

4. Archer, D. L., Bukovic-Wess, J. A., and Smith, B.G. Suppression of macrophage-dependent T-lymphocyte functions by gallic acid, a food additive metabolite. Proc. Soc. Exp. Biol. Med. 156:465, 1977.

5. Archer, D. L., Smith, B.G. and Bukovic-Wess, J. A. Use of an in vitro antibody-producing system for recognizing potentially immunosuppressive compounds. Int. Arch. All. Appl. Immunol. 56:90, 1978.

6. Archer, D. L. and Johnson, H. M. Blockade of mitogen induction of the interferon lymphokine by a phenolic food additive metabolite. Proc. Soc. Exp. Biol. Med. 157:684, 1978.

7. Archer, D. L., Smith, B. G. and Wess, J. A. Evidence for helper T-cell participation in the antibody response to thymus-independent antigens. IRCS Med. Sci. 6:76, 1978.

8. Archer, D. L. Immunotoxicology of foodborne substances: An overview. J. Food Prot. 41:983-988, 1978.

9. Archer, D. L. and Wess, J. A. Chemical dissection of the primary and secondary in vitro antibody response with gallic acid and butylated hydroxyanisole. Drug and Chem. Toxicol. 2:155-166, 1979.

10. Archer, D. L., Smith, B. G., Ulrich, J. T. and Johnson, H. M. Immune interferon induction by T-cell mitogens involves different T-cell subpopulations. Cell Immunol. 48:420-426, 1979.

11. Archer, D. L. Antioxidants and the immune response. Proc. of the Fourth FDA Science Symposium: Inadvertent modification of the immune response. pp. 99-103, 1980.

12. Archer, D. L., Smith, B. G. and Johnson, H. M. Effects of toxicants on T-cell subpopulations as determined by lymphokine activity. Arch. Toxicol. Suppl. 4:138-142, 1980.

13. Chen, S. E., Tse, C. S., Bernstein, I. L. and Archer, D. L. In vivo suppression and enhancement of the murine homocytotropic antibody response by staphylococcal enterotoxin A. Int. Arch. Allergy Appl. Immunol. 63:470-472, 1980.

14. Stelma, G. N. and Archer, D. L. Detection of low levels of staphylococcal enterotoxin A in foods by mitogenesis. IRCS Med. Sci. 8:347, 1980.

15. Bernstein, I. L., Gallagher, J. S., Johnson, H. M., Archer, D. L. and Splansky, G. L. Evaluation of reactions to tartrazine. Proc. IV FDA Science Symposium: Inadvertent modification of the immune response. pp. 258-260, 1980.

16. Archer, D. L., Smith, G. G. and Peeler, J. T. Activation of murine T-lymphocyte DNA synthesis in vivo by staphylococcal enterotoxin A: Applicability to immunotoxicity testing. IRCS Med. Sci. 8:457, 1980.

17. Osborne, L. C. and Archer D. L. The antiviral effect of human fibroblast interferon is blocked by gallic acid. IRCS Med. Sci. 8:756, 1980.

18. Stelma, G. N., Bradshaw, J. G., Kauffman, P. E. and Archer, D. L. Thermal inactivation of mitogenic activities of staphylococcal enterotoxin A at 121~C. IRCS Med. Sci. 8:629, 1980.

19. Archer, D. L., Smith, B. V. and Johnson, H. M. Direct and induced suppression of in vitro antibody production by selected phenols: A comparison to virus-type interferon. In Biological Relevance of Immune Suppression (Dean, J. and Padarathsingh, M., eds.) Van Nostrand, NY, pp. 199-212, 1981.

20. Archer, D. L., Wess, J. A., and Johnson, H. M. Inverse relationship between immune interferon induction and mitogen effects on the maturation of the primary antibody response. Immunopharmacology 3:71-81, 1981.

21. Archer, D. L. and Smith, B. G. Immunotoxic and immunosuppressive effects of food chemicals: Focus on diethylstilbestrol. Proceedings of the 33rd Annual Reciprocal Meat Conference of the American Meat Science Association, pp. 143-146, 1981.

22. Luster, M. I., Dean, J. H., Boorman, G. A., Archer, D. L., Lauer, L., Lawson, L. D., and Wilson, R. A. The immunotoxicity of orthophenyphenol, Tris (2,3-dichloropropyl) phosphate and cyclophosphamide following acute exposure in mice. Toxicol. and Appl. Pharmacol. 58:252-261, 1981.

23. Blalock, J. E., Archer, D. L., and Johnson, H. M. Anticelluar and immunosuppressive activities of foodborne phenolic compounds. Proc. Soc. Exp. Biol. Med. 167:391-393, 1981.

24. Osborne, L. C., Peeler, J. T. and Archer, D. L. Reduction in the antiviral activity of human fibroblast interferon by gallic acid. Infect. & Immun. 33:769-774, 1981.

25. Archer, D. L., Wess, J. A. and Smith, B. G. Location of specific lesions in the immune response using in vitro tests. Proc. Soc. Toxicol. Can. pp. 137-149, 1981.

26. Wess, J. A. and Archer, D. L. Restoration by cyclic guanosine monophosphate and extracellular calcium of butylated hydroxyanisole-suppressed primary murine thymus-dependent antibody response. Immunopharmacology 3:71-81, 1981.

27. Buxser, S. E., Boventre, P. F. and Archer, D. L. Specific receptor binding of staphylococcal enterotoxin by murine splenic lymphocytes. Infect. & Immun. 33:827-833, 1981.

28. Blakley, B. and Archer, D. L. The effect of lead acetate on the immune response of BDF1 mice. Tox. and Appl. Pharm. 61:18-27, 1981.

29. Archer, D. L. and Smith, B. G. Immunotoxicity testing of food chemicals: Different results may be obtained with in vitro and in vivo exposure to gallic acid. Proc. AOAC Symposium on Analytical Methodology for Determining Immunotoxicity of Chemicals Including Pesticides, 1982.

30. Archer, D. L., Smith, B. G., and Peeler, J. T. Analysis of in vivo and in vitro mitogen-induced T-cell activation: I. Disparate effects of diethylstilbestrol. J. Env. Pathol. Toxicol. & Oncol. 5:445-453, 1982.

31. Archer, D. L. New approaches to immunotoxicity testing. Env. Hlth. Persp. 43:109-113, 1982.

32. Archer, D. L., Smith, B. G. and Peeler, J. T. Analysis of in vivo and in vitro mitogen-induced T-cell activation: II. Studies on cyclophosphamide and application of in vivo activation to antiproliferative agents. J. Env. Pathol. Toxicol. & Oncol. 5:455-463, 1982.

33. Blakley, B., Archer, D. L. and Osborne, L. C. The effect of lead on immune and viral interferon production. Canad. J. Comp. Med. 46:43-46, 1982.

34. Wess, J. A. and Archer, D. L. Disparate in vivo and in vitro

immunomodulatory activities of Rhodamine B. Food and Chem. Toxicol. 20:9-14, 1982.

35. Blakley, B. R. and Archer, D. L. Mitogen stimulation of lymphocytes exposed to lead. Toxicol. and Appl. Pharmacol. 62:183-189, 1982.

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37. Wess, J. A. and Archer, D. L. Evidence from in vitro murine immunologic assays that some phenolic food additives may function as antipromoters by lowering intracellular cyclic GMP levels. Proc. Soc. Exp. Biol. Med. 170:427-430, 1982.

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C. MISCELLANEOUS PUBLICATION

000084

1. Archer, Douglas. 1994. Controlling Bacteria in Food Through Temperature, Fine Cooking Magazine, June/July Issue, 12-13.

2. Archer, Douglas. 1996. Should All Juices be Pasteurized? Food

Protection Inside Report, 2 pages.

3. Archer, Douglas. 2000. E. coli O157:H7 - Searching for Solutions. Food Technology 54:142.

4. Archer, Douglas. 2001. WHO Holds Food Safety Strategic Planning Meeting. Food Technology 55(5):22.

5. Archer, Douglas. 2001. Nitrite and the Impact of Advisory Groups. Food Technology 55(3):26.

6. Archer, Douglas. 2001. Can It Happen Again? Food Technology 55(9):28.

7. Archer, Douglas. 2001. The Flap Over Functional Foods. Food Technology 55(8):32.

8. Archer, Douglas. 2002. Global foodborne disease surveillance system faces hurdles. Food Technology 56(2):24.

9. Archer, Douglas. 2002. New technologies question the equality of pathogens. Food Technology 56(5):24.

D. **ABSTRACTS** (On request)

CURRICULUM VITAE

NAME: Donald H Hughes

DATE OF BIRTH

PLACE OF BIRTH.

EDUCATION

Institution	Degree	Year	Major Field
Cornell University, Ithaca, NY	B.S.	1956	Biochemistry
University of Delaware, Newark, DE	M.S.	1959	Biochemistry
University of Delaware, DE	Ph.D.	1961	Biochemistry

Ph D. Thesis — Isolation and characterization of constituents of the cultivated mushroom and their interaction with the browning enzyme polyphenol oxidase

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EXPERIENCE

Research & Development Department
Procter & Gamble Company
Cincinnati, Ohio

1960 - 1963	*Staff Scientist - Food Research*
1963 - 1965	Group Leader, Cake Mix Development
1965 - 1972	Section Head, Food & Enzyme Chemistry
1972 - 1978	Section Head, Corporate Toxicology
1978 - 1994	Scientific Coordinator, Chronic Health Effects

PATENTS ISSUED

Gallate Containing Liquid Shortening for Cake Mixes
D.H Hughes - 1971

Mushroom Nutrient Supplement
D.H. Hughes and H. Schumacher - 1971

Kojyl Acylate Containing Liquid Shortening for Cake Mixes
D.H. Hughes

Culinary Mixes Containing Fractionated Amylopectin and starch
D.H. Hughes, N.B. Howard, W. Bedenk - 1968

Granular Starch layer Cake Batter Systems
N.B. Howard, D.H. Hughes, R.G.K Strobel - 1966

Machine for Stem Cutting and Sizing of Mushrooms
D.H. Hughes, W.E. Larson - 1965

PROFESSIONAL MEMBERSHIPS

American Association for Advancement of Science
Sigma XI
Environmental Mutagen Society
British Mushroom Growers Association - Honorary Member
The Toxicology Forum - Member Board of Directors 1982 - 1994
The Toxicology Forum - Distinguished Fellow - 1994
The Toxicology Forum -- Consultant 1994 - Present
Society of Toxicology
International Society of Regulatory Toxicology and Pharmacology

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MISCELLANEOUS

Scientific.

- Advisor to USDA Southern Regional Labs as an Industrial Representative on the National Cottonseed Producers Association Subcommittee "Protein task Force", 1965-1969

- Chairman and Organizer of a Symposium on Enzyme Detergents for the Society of Industrial Microbiology held at the University of Rhode Island, 1970.

- Member of Committee to review Genetic Toxicology segment of the Food Safety Council report "Proposed System for Food Safety Assessment", 1979-80.

- Member of Scientific Committee of the American Industrial Health Council, 1977 - 1994. Vice Chairman 1986-1990, Chairman 1990-1994.

- Chairman of Risk Assessment Subcommittee of the American Industrial Health Council, 1979-1998.

- Co-Chairman of Society of Toxicology (SOT) Task Force to review the ED_{01} Megamouse Study, 1979-1981 Symposium held at National Meeting in San Diego, California, March 5, 1981

- Co-Chairman of SOT/NCTR ED_{01} Workshop Committee held at Mt. Sterling, Ohio, September 13-15, 1981.

- Chairman of a Controversies in Toxicology Session covering the National Toxicology Program's Carcinogenesis Bioassay at the Joint Meeting of ASPET/SOT in Louisville, Kentucky, August 1982.

- Member of NIEHS/NTP, Technical Report Review Committee on Carcinogens. 1988 -1989.

- NAS/NRC report on: "Carcingens and Anticarcinogens in the Human Diet". American Industrial Health Council liaison to: The Committee on Toxicity of Naturally Occurring Carcinogens, 1996.

- Program Coordinator for the Toxicology Forum, 1994-present. (Consultant.)

PUBLICATIONS

1. Carey, R.L , Hughes, D H Vacuum cooling experiments with fresh market mushrooms. Mushroom News 3, No. 10 (1957)
2 Hughes, D.H , Lynch, D.L., Somers, G.F. Chromatographic identification of the amino acids and carbohydrates in the cultivated mushroom Agaricus Campestris L. Ex Fries. J. Ag. And Food Chem. 6, No 11, 850-53 (1958)..
3. Lynch, D.L., Hughes, D.H., Rhodes, Y.E Jr.., Wright, L M. Effect of soil treatment practices on the amino acid composition of a sassafras silt loam. Misc. Paper #313 (1958).
4. Lynch, D.L , Hughes, D.H., Rhodes, Y.E Jr.., Pressure and gradient elution in ion exchange chromatography of the amino acids in soils. Soil Science 87 No. 5 , 339-44 (1959).
5. Larsen, W.E., Hughes, D.H.. Mushroom processing equipment - automatic washer and sponge drying line. Mushroom News 5, 9-11 (1959).
6. Hughes, D.H., Rhodes, Y.E. Jr. Changes in the amino acid composition of mushrooms with successive crops Mushroom Science IV 176 (1959).
7. Hughes, D.H, Sutton, C.L., Bull, R.L. The effects of various films on the shelf life of fresh mushrooms. Mushroom News 5, No. 10, 4-7 (1959).
8. Hughes, D.H. Preliminary characterization of the lipid constituents of the cultivated mushroom Agaricus Campestris. Mushroom Science V, 540-546 (1962).
9. Youngquist, R.W., Hughes, D.H , Smith, J.P. The effect of chlorine on starch-lipid interactions in flour. Abstract: American Oil Chemists Society, April 1968.
10. Howard, N.B., Hughes, D.H., Strobel, R.G.K. Function of the starch granule in the formation of layer cake structure. General Chemistry, Vol. 45, 329, 1968.
11. Hughes, D.H., McDermott, J.A , Quinlqn, P. Absorption, distribution and excretion of alkyl ethoxy sulfonates in the rat and man. Abstract: Society of Toxicology Proceedings, March 1975.
12. Bruce, R.D., et al Reexamination of the ED_{01} Study. Fundamental and Applied Toxicology 1: 26-128 (1981).
13. Barr, J.T., Hughes, D.H., Barnard, R.C. The use of risk assessment in decision making: Time for a review. Regulatory Toxicology and Pharmacology 1: 264-276 (1981).
14. Hughes, D.H., et al. A report on the workshop on biological and statistical implications of the ED_{01} study and related data bases. Fundamental and Applied Toxicology. 3: 127-160 (1983).
15. Over twelve technical publications on mushroom technology.
16. Ashby, J. Et al., A Scheme for Classifying Carcinogens. Regulatory Toxicology and Pharmacology 12 270-295. (1990)

SUBMISSION END

AM

Ricker, Karin

From: James Barnett [jbarnett@aacgroup.com]
Sent: Wednesday, August 06, 2003 3:04 PM
To: Ricker, Karin; Belay, Negash
Cc: Dick Alsmeyer (E-mail); Hirotaka Furukawa; Ed Steele
Subject: FW: Notice of GRAS Filing

Drs. Ricker and Belay:
The responses to your questions are provided below. If you have any other questions, feel free respond.
Jim Barnett
512-266-2620

-----Original Message-----
From: Hirotaka Furukawa [mailto:hirosfo@abox23.so-net.ne.jp]
Sent: Tuesday, August 05, 2003 10:18 PM
To: James Barnett
Cc: Sikeuchi@aol.com; O.Muramae CHISSO; ?? ??; Jun Hiraki; Dick Alsmeyer (E-mail)
Subject: Re: Notice of GRAS Filing

Dear Dr. Barnett

Thank you for your inquiry.
Regarding the questions, our answers are as follows:

1) The production strain at present is Streptomyces albulus ssp. lysinopolymerus strain (FERM BP-5926). This strain has been already deposited in National Institute of Bioscience and Human-Technology Agency of Industrial Science and Technology in 1996. The institute's name has been changed IPOD (International Patent Organism Depositary) now.

2) We also suppose it is Amberlite XT-1006 as you assumed. We have not used Amberlite XP-100. Do you need the information about XT-1006?

3) The proposed mechanism of the inhibitory effect of e-polylysine is suggested as an electrostatic adsorption of e-polylysine to the surface of microorganisms. It is based on the molecule's cationic properties and leads to stripping of the outer membrane and abnormal distribution of the cytoplasm. This has been observed by electron microscopy. Attached herewith, please find the publication by Dr. Shima et al. (1984).
I have also attached the article about preservation of rice by polylysine preparations.
If you have any question or need more information, please feel free to contact me.

Best regards,

Hirotaka Furukawa

----- Original Message -----
From: James Barnett

To: Hirotaka Furukawa
Sent: Tuesday, August 05, 2003 1:49 AM
Subject: RE: Notice of GRAS Filing

000095

Dear Dr. Furukawa:

I just received a phone call regarding the GRAS submission from Dr. Karin Ricker and she had a few questions. Unfortunately, I have packed up my papers for an impending move to Texas and am unable to research these issues readily and some are unknown to me.

1) Is the current name of the production strain Streptomyces albulus ssp. lysinopolymerus strain 346 or is there another strain name for the mutant now used in production? Has the strain been deposited or registered in any culture collection like ATCC? If yes, which collections?
2) They asked about Amberlite XP-100, a product for which they are unfamiliar. What is this material, who supplies it and is that the correct designator? I assume it is an ion-exchange resin of some type. (I could not find this designator in a search of the GRAS document; possibly Amberlite XT-1006?)
3) Lastly, they would like further confirmation of the antimicrobial mechanism of action as a cationic inhibitor. Possibly information from the Hiraki et. al., 1998 paper or other sources. Further, would it be possible to supply them with the studies you conducted on various foodstuffs showing microbial inhibition? These would not be held as confidential if submitted to FDA. I hope that is not a problem, but please advise if you have any concerns about submitting them. I will fax the studies to FDA next week if you approve.

Thank you for your help with this inquiry.

Jim Barnett
772-321-1922 (Cell)

-----Original Message-----
From: Hirotaka Furukawa [mailto:hirosfo@abox23.so-net.ne.jp]
Sent: Sunday, August 03, 2003 8:42 PM
To: James Barnett
Subject: Re: Notice of GRAS Filing

Dear Dr. Barnett

I have received your email and thank you for your information.
We are very excited to hear the good news.
Your further cooperation in this project will be much appreciated.

Best regards,

Hirotaka Furukawa

----- Original Message -----
From: "James Barnett" <jbarnett@aacgroup.com>
To: "Dick Alsmeyer (E-mail)" <alsmeyer.rockport@erols.com>; "Hirotaka Furukawa" <hiro.furukawa@chisso.co.jp>
Cc: "Gary Flamm" <wgflamm@attglobal.net>
Sent: Saturday, August 02, 2003 5:09 AM
Subject: Notice of GRAS Filing

000096

Pages 000097 - 000106 have been removed in accordance with copyright laws. Please see appended bibliography list of the references that have been removed from this request.

Pages 000107 - 000113 have been removed in accordance with copyright laws. Please see appended bibliography list of the references that have been removed from this request.

AM

Ricker, Karin

From: Hirotaka Furukawa [hirosfo@abox23.so-net.ne.jp]

Sent: Tuesday, August 12, 2003 3:50 AM

To: Ricker, Karin; Belay, Negash

Cc: Dick Alsmeyer (E-mail); O.Muramae CHISSO; Hayakeyama Masakazu CHISSO; Jun Hiraki; James Barnett; Ed Steele

Subject: Re: Amberlite

Dear Dr. Belay,

In reply to your request about Amberlite XT1006, we are pleased to attach the MSDS.
If you need further information, please let us know.

Regarding the answer of August 5, the year when the production strain was deposited, was 1995.
I deeply apologize for our mistake.

Yours very truly,

Hirotaka Furukawa
Meitetsu Inc.

----- Original Message -----
From: "James Barnett" <jbarnett@aacgroup.com>
To: "Hirotaka Furukawa" <hiro.furukawa@chisso.co.jp>
Cc: "Ed Steele" <esteele@aacgroup.com>
Sent: Tuesday, August 12, 2003 1:56 AM
Subject: FW: Amberlite

> Dear Dr. Furukawa:
> Please respond to inquiry from FDA regarding Amberlite XT 1006..
> Thank you
> Jim Barnett
>
> -----Original Message-----
> From: Belay, Negash [mailto:Negash.Belay@cfsan.fda.gov]
> Sent: Monday, August 11, 2003 10:43 AM
> To: 'James Barnett'
> Cc: Ricker, Karin
> Subject: RE: Amberlite
>
> Dear Dr. Barnett,
>
> We need further clarification regarding Amberlite XT 1006. The substance is
> referred to in the notice by its trade name and your response to our request
> for clarification simply expanded on the trade name. Our regulations list
> resins by their chemical name, not trade name, so we need the chemical name
> for Amberlite XT 1006 to properly identify it. Please provide this
> information at your earliest convenience.
>
> Thank you.
>
> Negash Belay
>
>

000114

> -----Original Message-----
> From: James Barnett [mailto:jbarnett@aacgroup.com]
> Sent: Thursday, August 07, 2003 7:31 AM
> To: Belay, Negash
> Cc: Ed Steele; Hirotaka Furukawa
> Subject: Amberlite
>
> Dr. Belay:
> As you have received, I sent an e-mail yesterday responding to questions Dr.
> Ricker had asked regarding the e-polylysine GRAS submission. I must have
> heard her wrong on our phone call regarding the name of the Amberlite ion
> exchange resin you wanted more information on. It isn't Amberlite XP-100
> apparently. What is the correct name?
> Thanks
> Jim Barnett
>

MATERIAL SAFETY DATA SHEET
Rohm and Haas Company

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

AMBERLITE™ XT1006

MSDS Date : 02/29/00

COMPANY IDENTIFICATION
ROHM AND HAAS COMPANY
100 INDEPENDENCE MALL WEST
PHILADELPHIA, PA 19106-2399

EMERGENCY TELEPHONE NUMBERS

HEALTH EMERGENCY	: 215-592-3000
SPILL EMERGENCY	: 215-592-3000
CHEMTREC	: 800-424-9300

2. COMPOSITION/INFORMATION ON INGREDIENTS

No		CAS REG NO	WEIGHT (%)
1	Sulfonated divinylbenzene/styrene copolymer, Na ion form	Not Required	66 - 70
2	Water	7732-18-5	30 - 34

See Section 8, Exposure Controls / Personal Protection

3. HAZARDS IDENTIFICATION

Primary Routes of Exposure

Skin Contact
Eye Contact

Eye Contact

Material can cause the following:
- slight irritation

Skin Contact

Prolonged or repeated skin contact can cause the following:
- slight skin irritation

4. FIRST AID MEASURES

Eye Contact

Flush eyes with a large amount of water for at least 15 minutes. Consult a physician if irritation persists.

Skin Contact

Wash skin thoroughly with soap and water.

000116

5. FIRE FIGHTING MEASURES

Unusual Hazards

Combustion generates toxic fumes of the following:
- sulfur oxides

Extinguishing Agents

Use the following extinguishing media when fighting fires involving this material:
- carbon dioxide - dry chemical - water spray

Personal Protective Equipment

Wear self-contained breathing apparatus (pressure-demand NIOSH approved or equivalent) and full protective gear.

6. ACCIDENTAL RELEASE MEASURES

Personal Protection

Wear gloves made of the following material:
- cotton, canvas or leather

Additional personal protective equipment should include the following:
- safety glasses (ANSI Z87.1 or approved equivalent)

Procedures

Floor may be slippery; use care to avoid falling. Transfer spilled material to suitable containers for recovery or disposal.

7. HANDLING AND STORAGE

Storage Conditions

Avoid temperature extremes during storage; ambient temperature preferred. Avoid repeated freeze-thaw cycles; beads may fracture. If frozen, thaw at room temperature.

Handling Procedures

NOTE: This product as supplied is a whole bead resin and may produce slight eye irritation. However, the ground form of this resin should be treated as a severe eye irritant. Worker exposure to ground resins can be controlled with local exhaust ventilation at the point of dust generation, or use of suitable personal protective equipment (dust/mist air-purifying respirator and safetygoggles). Properly designed equipment is vital if these resins are to be used in conjunction with strong oxidizing agents such as nitric acid to prevent a rapid build-up of pressure and possible explosion. Consult a source knowledgeable in the handling of these materials before proceeding. Avoid to pack columns with dry resins. Dry beads may expand when wetted and that expansion can cause breakdown of columns. Precaution must be taken to wet dry beads.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Exposure Limit Information

No		CAS REG NO	WEIGHT (%)
1	Sulfonated divinylbenzene/styrene copolymer, Na ion form	Not Required	66 - 70
2	Water	7732-18-5	30 - 34

Comp.		ROHM AND HAAS		OSHA		ACGIH	
No.	Units	TWA	STEL	TWA	STEL	TWA	STEL
1		None	None	None	None	None	None
2		None	None	None	None	None	None

Respiratory Protection

A respiratory protection program meeting OSHA 1910.134 and ANSI Z88.2 requirements or equivalent must be followed whenever workplace conditions warrant a respirator's use. None required under normal operating conditions.

Eye Protection

Use safety glasses (ANSI Z87.1 or approved equivalent).

Hand Protection

Avoid skin contact. When using this substance, use skin protection. - Cotton, canvas, or leather gloves
Gloves should be removed and replaced immediately if there is any indication of degradation or chemical breakthrough.

Engineering Controls (Ventilation)

The ventilation system employed is dependent on the user's specific application of this material. Refer to the current edition of Industrial Ventilation: A Manual of Recommended Practice published by the American Conference of Governmental Industrial Hygienists for information on the design, installation, use, and maintenance of exhaust systems. None required under normal operating conditions.

Other Protective Equipment

Facilities storing or utilizing this material should be equipped with an eyewash facility.

9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance	Clear and opaque
State	Beads
Melting Point	0°C/32°F Water
Boiling Point	100°C/212°F Water
Solubility in Water	Insoluble
Percent Volatility	30 to 34 %

See Section 5, Fire Fighting Measures

000118

10. STABILITY AND REACTIVITY

Instability

This material is considered stable under specified conditions of storage, shipment and/or use. See SECTION 7, Handling And Storage, for specified conditions. However, avoid temperatures above 190C.

Hazardous Decomposition Products

Thermal decomposition may yield the following:
- monomer vapors - sulfur oxides

Hazardous Polymerization

Product will not undergo polymerization.

Incompatibility

Avoid contact with strong oxidizing agents, particularly concentrated nitric acid.

11. TOXICOLOGICAL INFORMATION

Acute Data

Toxicity data for a compositionally similar material are listed below.

Oral LD50 - rat: >5000 mg/kg
Dermal LD50 - rabbit: >5000 mg/kg

Mutagenicity Data

Ames mutagenicity: Non-mutagenic

12. ECOLOGICAL INFORMATION

No Applicable Data

13. DISPOSAL CONSIDERATIONS

Procedure

Unused resin may be incinerated or landfilled in facilities meeting local, state, and federal regulations. For contaminated resin, the user must determine the hazard and use an appropriate disposal method.

14. TRANSPORT INFORMATION

No Applicable Data

15. REGULATORY INFORMATION

Workplace Classification

000119

This product is considered non-hazardous under the OSHA Hazard Communication Standard (29CFR 1910.1200).

This product is not a 'controlled product' under the Canadian Workplace Hazardous Materials Information System (WHMIS).

SARA TITLE 3: Section 311/312 Categorizations (40CFR 370)

This product is not a hazardous chemical under 29CFR 1910.1200, and therefore is not covered by Title III of SARA.

SARA TITLE 3: Section 313 Information (40CFR 372)

This product does not contain a chemical which is listed in Section 313 at or above de minimis concentrations.

CERCLA Information (40CFR 302.4)

Releases of this material to air, land, or water are not reportable to the National Response Center under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) or to state and local emergency planning committees under the Superfund Amendments and Reauthorization Act (SARA) Title III Section 304.

Waste Classification

When a decision is made to discard this material as supplied, it does not meet RCRA's characteristic definition of ignitability, corrosivity, or reactivity, and is not listed in 40 CFR 261.33. The toxicity characteristic (TC), however, has not been evaluated by the Toxicity Characteristic Leaching Procedure (TCLP).

United States

All components of this product are produced in compliance with the requirements of the U.S. Toxic Substances Control Act (TSCA) and are either listed on or are exempt from listing on the Inventory. For certain polymeric substances, the Polymer Exemption cited at 40 CFR 723.250 may apply.

16. OTHER INFORMATION

Rohm and Haas Hazard Rating		Scale
Toxicity	1	4=EXTREME
Fire	1	3=HIGH
Reactivity	0	2=MODERATE
Special	-	1=SLIGHT
		0=INSIGNIFICANT

Ratings are based on Rohm and Haas guidelines, and are intended for internal use.

HMIS Hazard Ratings

HMIS Hazard Ratings: HEALTH =1, FLAMMABILITY =1, REACTIVITY =0
PERSONAL PROTECTION; See Section 8, Exposure Controls/Personal Protection for recommended handling of material as supplied; check with supervisor for your actual use condition.
Scale: 0 = Minimal, 1 = Slight, 2 = Moderate, 3 = Serious, 4 = Severe
* = Chronic Effects (See Section 3, Hazards Identification)

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HMIS is a registered trademark of the National Paint and Coatings

Association.

ABBREVIATIONS:

ACGIH	= American Conference of Governmental Industrial Hygienists
OSHA	= Occupational Safety and Health Administration
TLV	= Threshold Limit Value
PEL	= Permissible Exposure Limit
TWA	= Time Weighted Average
STEL	= Short-Term Exposure Limit
BAc	= Butyl acetate

Bar denotes a revision from previous MSDS in this area.

AM 

Ricker, Karin

From: James Barnett [jbarnett@aacgroup.com]
Sent: Tuesday, September 16, 2003 9:45 AM
To: Ricker, Karin
Cc: Ed Steele; Hirotaka Furukawa
Subject: FW: GRN 135- additional question

Dr. Ricker:
Dr. Furukawa has replied below and agreed that the specification for lead will be set at 0.5 ppm. I hope this is acceptable. Please respond if you have further questions.
Jin Barnett

-----Original Message-----
From: Hirotaka Furukawa [mailto:hirosfo@abox23.so-net.ne.jp]
Sent: Monday, September 15, 2003 4:34 AM
To: James Barnett
Subject: Re: GRN 135- additional question

Dear Dr. Barnett

Thank you for your continuing help.
I have received the answer from our tokyo office about this matter.
We can change the lead specification to 0.5ppm, because it (5ppm) is not the actual level.
If you have any suggestion, please let me know.
Thank you.

Best regards,

Hirotaka Furukawa

----- Original Message -----
From: James Barnett

To: Hirotaka Furukawa
Sent: Wednesday, September 10, 2003 10:49 PM
Subject: FW: GRN 135- additional question

Dear Dr. Furukawa:
Thank you for your excellent responses to FDA's questions recently. Dr. Ricker has questioned the specification for lead (see below). Do you have any data or can the specification be lowered? Please respond with your thoughts.

Best regards,

Jim Barnett

-----Original Message-----
From: Ricker, Karin [mailto:Karin.Ricker@cfsan.fda.gov]
Sent: Wednesday, September 10, 2003 8:01 AM
To: 'jbarnett@aacgroup.com'

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Cc: Edelstein, Rebecca L
Subject: GRN 135- additional question

Hello Jim-
We do have another question- can you please follow up with this as well?
One of our reviewers noticed that the lead specification (5 ppm) is too high. Are these the actual levels? Can the lead specification be lowered ? (0.5 ppm or 0.1 ppm would be good).

Thanks so much for your help.
Regards, Karin

Karin Ricker, Ph.D.
Consumer Safety Officer
Division of Biotechnology & GRAS Notice Review
Office of Food Additive Safety
CFSAN, FDA
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College Park, MD 20740-3835
Ph. 202-418-3403

Reference List for Industry Submission, GRN 000135

Pages	*Author*	*Title*	*Publish Date*	*Publisher*	*BIB_Info*
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000097 - 000106	Fukushi, Hideaki; Hiraki, Jun	Preservation of Cooked Rice With Polylysine	NA	Monthly Food Chemicals	NA
000107 - 000113	Shima, Shoji; Matsuoka, Hiroyoshi; Iwamoto, Toshiro; Sakai, Heiichi	Antimicrobial Action of Epsilon-Poly-L-Lysine	November 1984	The Journal of Antibiotics	Volume XXXXVII, Number 11, pgs 1449-1455

NA- Not applicable